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WATER EXCHANGES DUE TO ANESTHETIC DRUGS * †

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A TENDENCY to belittle or ignore the familiar has no better example in physiology than in the general attitude toward water. Water is everywhere. In the processes of life no substance is more useful; accordingly, it is continually subject to promiscuous taking or leaving. It enters or leaves the body in accord with the physical conditions of the moment, responding in the one case to thirst or to a dry surface, and in the other to osmotic conditions in the kidney and lungs or to the relations between the body and its environment as regards vapor pressure. It is difficult to conceive of chemical changes within the body without movement of water, which is pushed and pulled about in the service of all other molecules from the smallest electrolyte to the largest colloid, a slave of physical laws.

When we inquire, however, what interest attaches to a substance so humble and so ubiquitous, the importance of water begins to emerge. A non-compressible yet pliable building material, a vehicle for distribution, a medium for metabolic exchange, and a powerful equalizer of temperature, it exhibits manifold indispensability. In conditions involving profound changes of function new water patterns are to be expected; we may therefore seek them in the field of anesthesia.

In anesthesia the significance of water may be considered under three heads. One may consider first its role in the process of action of an anesthetic agent upon the cells. This concerns its behavior during the suppression of cell function as well as the question as to whether it is a causal factor. So-called "theories of dehydration" have been built upon the latter possibility.

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The second head concerns water movement anywhere in the body, arising from the fact that certain central nerve cells have become anesthetized. This involves the states of hydration of the blood and tissues with their bearings on impairment of the circulation, especially when this leads to shock. Again, there are the shifts of water concerned with the regulation of body temperature as well as those associated with renal activity.

Finally, there are movements of water concerned with the distribution and fate of the anesthetic drug itself. Little is known of this subject and perhaps little need be for the present, but a closer view, for example, of the destruction of certain barbiturates in the body should yield information.

Knowledge is so fragmentary today in all of the above fields that a systematic and satisfying discussion is out of the question. Bits of information, however, gleaned in my own laboratories and elsewhere, tend to illuminate this large problem in pharmacology which is crying out for orderly solution. For the patient the expected value of such an accomplishment needs no elaboration at this time and place. It is preferred rather to devote attention directly to the water exchanges in nerve cells and elsewhere.

Some of the pertinent findings have been made in connection with the development of so-called "theories of narcosis" or, more properly, of anesthesia. Let us view them, however, essentially as facts, for, as Beecher (1) (1938) has aptly pointed out, the material is as yet inadequate for constructing a really complete theory of anesthesia.

Even Kurt Meyer (2) (1937), in adducing recently an extraordinary group of experimental facts in support of the views of his late father, frankly says of the Meyer-Overton lipoid theory: "It is not really a theory which explains the mechanism of narcosis, but rather the expression of an experimentally observed regularity, a rule of which every theory must take account." According to Meyer, "Narcosis commences when any chemically indifferent substance has attained a certain molar concentration in the lipoids of the cell (or, to be more precise, in the lipoidic alcohols of the cell substance). This concentration depends on the nature of the animal or cell, but is independent of the narcotic used."

The concentration just designated Meyer now sets at about .03 molar. The "lipoidic alcohols" to which he refers are typified by cholesterol and are represented in his latest artificial system by oleic alcohol. The use of this substance in place of fats has enabled him to extend quantitative agreement to a lot of "polar" substances, especially alcohols and amides.

The contrast drawn by Meyer between polar and non-polar anesthetic agents is dwelt upon because the latter substances represent a class capable of displacing water from alcoholic lipoids, illustrating,

for some but not all anesthetic substances, a possible mechanism of dehydration.

The lipoid "rule" is not claimed to concern the problems of membranes. It does, however, demonstrate certain facts with which a number of other so-called "theories of narcosis" are in many respects compatible. For example, consider the standpoint of Quastel and his group (3) (1939) who, extending Warburg's "adsorption theory," hold that anesthetics interfere directly with the function of some components or component of intracellular oxidizing systems. The *lipoids,* while concerned with the affinity of the cell for anesthetics, need not play a direct role in the inhibition of oxidation. It has been found convenient to assume rather that this lipoid-anesthetic combination tends to densify the cell, sufficiently to interfere with permeability and a free exchange of nutrients, metabolites and water.* Release of water by the cells is supposed by Spiegel and Spiegel-Adolf (4) (1938) to result from a process in which anesthetic agents diminish the surface tension of lipoid particles, thereby lessening their water-binding capacity. Thus permeability for electrolytes would be decreased and function embarrassed. It should be mentioned, however, that all anesthetics are not surface-active.*

"Dehydration" or "Colloid" Theories of Anesthesia.—Ranke (5) (1867) observed that clear saline extract of muscle or of nerve substance became clouded on the addition of either chloroform, ether, or amylene, and stated his belief that this effect provided the key to the physiological understanding of the influence of these substances upon the organism. Claude Bernard (6) in 1875 attributed depression of function in anesthesia to the semicoagulation of protein. This meant a degree of coagulation which was still reversible. Binz (7) (1877) thought it significant that 1 per cent. morphine in solution coagulates cells. In recent years Bernard's theory has been championed by Bancroft (8) (1931) and his school who dogmatically attempted to assign to physiological function a state of "peptization" and to suppression of function a state of "aggregation." This involves respectively hydration and dehydration; when aggregation occurs water is extruded. It is to be remarked that the water change here envisioned may precede the change in function, thus conceivably contributing to the depression.

Dubois (9) in 1882 associated anesthetic action with dehydration because he saw plants transude water in the presence of chloroform vapor. This process, however, was not reversible. Stephanowski (10) in 1902 stated that chloroform increased the vacuoles in Vorticella, a reversible process which implied loss of water from the cell body. Knaffl-Lenz (11) in 1918 showed that low concentrations of alcohol, aromatic amides and ether shrink red blood cells, with loss of water, thereby diminishing permeability. He considered this to be a logical model of anesthetic action. Some ten years previously Höber

* Cf. Hirschfelder, A. D., and Searles, E. R., J. Pharm. Exper. Therap., 29, 441–448, 1926.

(12) (1907), a well-known physical chemist, had associated shrinkage of cells with anesthesia. Clearly, with protein coagulation or colloidal aggregation water tends to be lost from the colloidal system and it has often been pointed out that this may well create a state of decreased permeability of the cells to water soluble substances. Comparison has been made with astringent action.

Kochmann (13) (1923) has made intriguing experiments in support of the analogy between dehydration and anesthesia. Imitating the technique of Martin H. Fischer, he produced swelling of fibrin, either by distilled water or by N/100 HCl. He then repeated the experiments in the presence of various anesthetic drugs. These anesthetics decreased the swelling of fibrin, thereby exhibiting dehydration. The process was reversible, removal of the anesthetic allowing an increase in the swelling. Kochmann next studied the irritability of frog muscle under the influence of a great variety of alcohols and other anesthetics, including chloroform, chloral and ethyl methane. In every case, the threshold concentration of the anesthetic for abolishing irritability from the frog muscle effected a loss of water from the muscle. This was demonstrated by weight losses ranging from 2 to nearly 11 per cent. Kochmann postulated for anesthesia the presence of substance with both lipoid and water solubility, which would promote adsorption to lipoid-containing cells, leading within the cell to reversible dehydration of the cell colloids, decreasing permeability and thereby decreasing metabolism and function.

Like Kochmann, Sivadjians (14) (1933) found inhibition of the swelling of muscle (turtle) in proportion to the strength of any anesthetic which was present. These significant experiments on muscle are compatible with the extensive work being done today on intra- and extra-cellular water and ions in connection with muscle activity. Fenn (15) (1939), for example, has shown that the limb muscles of cats take up water in response to nerve stimulation *in vivo*; Wood, Collins and Moe (16) (1940) have recently described a heart-lung-gastrocnemius preparation from a dog in which indirect tetanic stimulation of the muscle resulted in a rapid gain of water, while Miller and Darrow (17) (1940) have obtained like effects in rats. All these facts point to the gain of water by increasingly active cells and its loss by cells exhibiting diminished activity. No causal connection is thereby established, but the increase of metabolites associated with increased function would be expected to exert osmotic force from within the cell, the opposite effect taking place with lowered metabolism. This sort of water change evidently follows rather than precedes the alteration of function.

The question of cellular water exchanges in connection with anesthetic agents first enlisted my own interest during studies of morphine withdrawal at the University of Louisville. In rats, withdrawal of morphine led to increasing the water content of the brain, although the blood was in general dehydrated. The experiments were done by com-

paring animals as nearly alike as possible, some of which were drugged, the others serving as normal controls. The work was extended to a litter of young dogs one of which was killed after a seven weeks course of morphine, another the day following withdrawal after a similar period of addiction, another on the third day of withdrawal, and the fourth while quite normal. Both dogs withdrawn from morphine showed

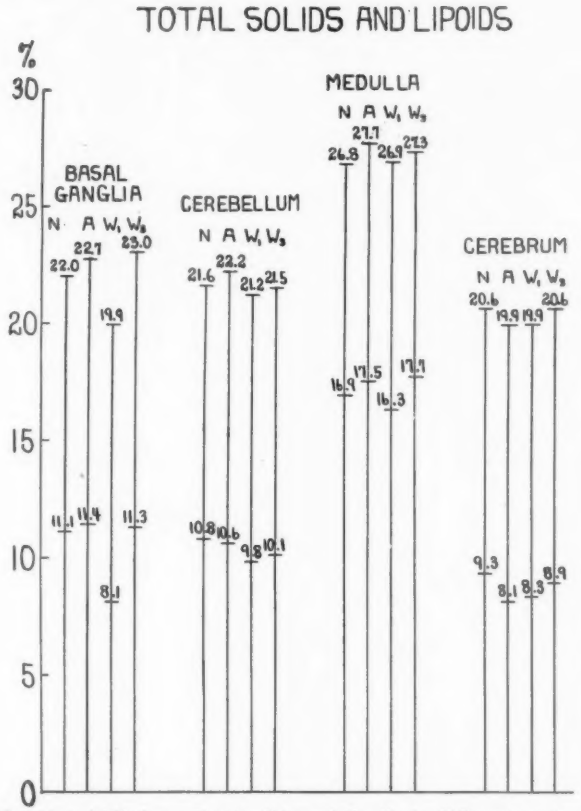

FIG. 1. Morphine Addiction. Total solids and lipoids in different parts of brains of a litter of dogs. Ordinates: solids per cent. and lipoids per cent. *N*, normal dog; *A*, 49th day of addiction; W_1, first day of withdrawal; W_3, third day of withdrawal. Upper figures, total solids; lower figures, total lipoids.

marked concentration of both serum and whole blood on the first day, while the dog killed on the first day of withdrawal exhibited the wettest brain of all as regards especially the basal ganglia and cerebrum (Fig. 1). These findings may in part be related to the state of tremor exhibited by such dogs as a result of withdrawal of the morphine. A sort of reversed narcosis or hyperactive condition was thus associated with brain hydration.

The brain water was next measured in anesthetized rats selecting not only morphine, but also amytal and ether as anesthetic agents. The experimental results are shown in Fig. 2 (1931). Therein are shown respectively by ordinates and abscissae the water content of medulla and cerebrum of rats. Each arrow leads from a point plotted from determinations on the normal state to one from conditions during anesthesia. As determinations cannot be made both before and during anesthesia on the same animal, the results are shown further with respect

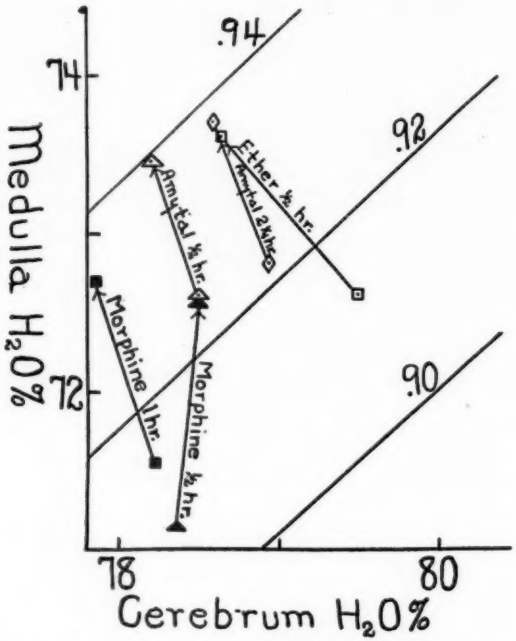

FIG. 2. Changes in Water Content of Cerebrum and Medulla in Rats Before and After Morphine, Amytal, or Ether. Ordinates: medulla water per cent.; abscissae: cerebrum water per cent. Diagonals: ratio medulla water/cerebrum water. The arrows lead from the preanesthetic determinations in normal rats to those in anesthetized litter-mates. (Illustration reproduced by permission of *Science*.) Science, 73, 346–347, 1931.

to the medulla water/cerebrum water ratio (cf. diagonal lines). This makes it possible to compare with one another rats in unavoidably differing degrees of hydration at the time of the experiment. The significance of this ratio also was conjectured to have a bearing upon the movement of water into or out of cells, this for the reason that the cerebrum is considerably richer in cells than is the medulla. Fifteen normal rats exhibited a medulla water/cerebrum water ratio of .922 $\pm$ .003, whereas thirteen rats after morphine sulphate showed a ratio of .939 $\pm$ .007. Amytal, in the case of five rats, and ether in a rat and two

rabbits, were followed by smaller increases in the ratio. During the stage of ether excitement, a ratio of .928 was shown and during muscular activity .924, whence it was argued that complete anesthesia is associated with the only significantly increased ratios. Anesthesia therefore is accompanied by a net movement of water from cerebrum to medulla, strongly suggesting brain cell dehydration.

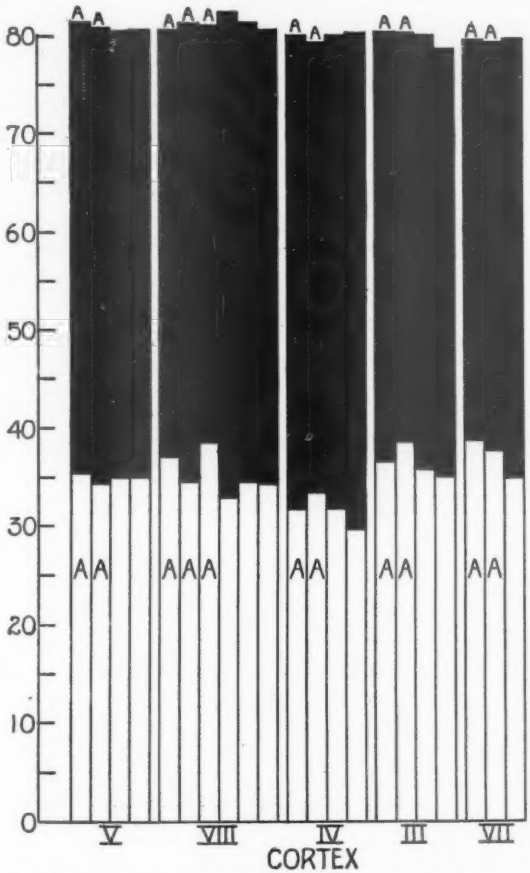

FIG. 3. Water of Brain Cortex in Rabbits. Determinations in litters arranged in order of size (and age) from left to right (one to three kilos). Columns show total water in per cent of tissue; solid parts: intracellular; open parts: extra-cellular. All columns marked A are from amytal treated rabbits, others were normal. Ordinates: per cent water.

This question has been approached more directly during the past few months in the Yale Laboratory of Pharmacology by Brezina, Gallup and myself. Attention was confined to the effect of amytal upon rabbits. These animals were studied by comparison of litter mates simul-

taneously sacrificed, one hour after the administration of amytal to one half the group. We began with total water determinations in the cortex and medulla respectively. In each of five litters comprising twenty-one rabbits in all, confirmation of increase in the medulla water/cortex water ratio was definite. The following changes in the individual litters were noted (the number of rabbits being shown in parentheses): from .900 (2) to .906 (2); from .911 (2) to .920 (2); from .902 (2) to .922 (2); from .905 (1) to .910 (2); from .923 (3) to .958 (3). As in the earlier experiments there was a large increase in the medulla water with usually a very slight decrease in the water of the cortex.

More direct evidence for the behavior of the cells with respect to water was sought in studies of intra- and extracellular water in the cortex. Chlorides were determined in the plasma and cortex of the sacrificed animals, which in conjunction with the total water of the cortex furnished data for the calculation of intra- and extracellular water in each case. The results are shown in Fig. 3 for five litters of rabbits. Amounts of water are indicated by column heights. In each litter, the amytal rabbits are represented by the letter *A*, the results being given at the left of the control litter mates. By arrangement of the litters in order of age, beginning from the left hand, the general water loss with growth from about one to three kilos body weight is shown. In total cortical water, represented by the total height of each column, no constant change was observed as a result of amytal anesthesia. The amounts of extracellular water are shown in the open columns at the bottom, and of intracellular water in the solid blocks at the top. For the oldest four litters there will be seen a constant tendency for the extracellular water to increase as a result of the administration of amytal. In the case of the youngest litter, the atypical results may be explained by the fact that these animals became deeply anesthetized within five or ten minutes whereas the time required for the older animals was twenty minutes or longer. It is believed that when the animals were sacrificed at the end of the standard period of one hour they were already on the road to recovery from anesthesia, and were therefore not strictly comparable with the elder group.

The above results seem to show conclusively that amytal anesthesia is associated with movement of water from the cells of the cortex to the extracellular spaces, indicating shrinkage of the cortical cells. Our results are considered exceedingly significant because they indicate, not changes in some model system, but shrinkage of brain cells of living animals exposed to anesthesia. Never before, to our knowledge, has dehydration of the nervous system during anesthesia been so directly demonstrated.

As for the effects of anesthesia upon water shifts, elsewhere than in the central nervous system, we may consider first the blood. In 1924 Wesley Bourne and I (18) confirmed, with more appropriate procedures, the findings of earlier workers that increased concentration of

the blood appears during ether anesthesia, and found that in dogs in the first plane of the third stage of anesthesia, this concentration amounted to ten or fifteen per cent., regardless of considerable changes in environmental and therefore of body temperature. The animals were made practically poikilothermous by ether with the constantly elevated blood concentration, the water shifting movements in response to temperature being among the eliminated reflexes. Blood concentrations of this order of magnitude were later confirmed in specific gravity changes by Dr. James Winter and myself for dogs and later by Dr. Paul Twaddle (19) (1935) for rabbits. Twaddle found the spleen not implicated in this species but in dogs its contraction contributes to the whole blood concentration (Searles (20) 1938, 1939). Since Barcroft's (21) work (1925) demonstrating the role of the spleen as a large flexible reservoir under various conditions, it has been recognized that the blood concentration under ether could be largely accounted for by extrusion of cells from the spleen. Water shifts independent of the spleen, and apparently affecting the concentration of the plasma, have been reported for ether anesthesia. In our laboratory two very carefully controlled periods of anesthesia in two rabbits yielded no change whatever in the plasma concentration, and we believe therefore that ether anesthesia need not involve net movement of water in or out of the blood. The above described changes and some related effects of ether are compared with the effects of morphine and amytal in the Table. Presumably the findings therein shown for ether apply in general to chloroform, urethane, and other substances while morphine and amytal are typical respectively of the opiates and barbiturates.

TABLE

COMPARISON BETWEEN ETHER, MORPHINE AND AMYTAL AND COLD AS TO WATER SHIFTS AND SOME RELATED CHANGES

	Ether	Morphine	Amytal	Cold
WATER				
Blood	−−	−	++	−
Plasma	0	−	++	−
Medulla (and M/C)	+	+	+	
Liver	+		++	+
INTRACELLULAR WATER	0			
Liver			−	+
Cerebrum			−	
Skinned Animal			−	+
Spleen size	−−	−	+	+
Cortex pH	7.1	7.1	7.25	
Lactic acid of brain	−		−	
PO_4/phospho-creatine of brain			−	
Electrocorticogram	−−−	−−	−	
Cortex vessels	+		0	
Hypothalamus vessels	0		+	−?

Morphine in cats exhibits a loss of water from both whole blood and plasma (Twaddle), a phenomenon also occurring on withdrawal of morphine from long addicted animals (Barbour, Russell, Flowers, Dunham and Hunter (22), 1929). In the barbiturates group Bourne, Bruger and Dreyer (23) (1930) showed definitely that amytal dilutes to a considerable extent both blood and plasma. These investigators showed further that a marked increase in spleen size occurs in dogs under amy-

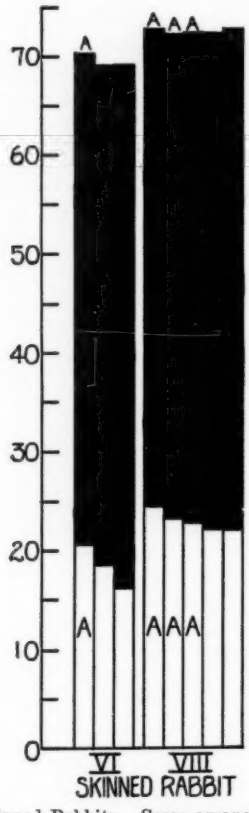

FIG. 4. Water of Skinned Rabbits. Same arrangements as in Fig. 3.

tal. Adolph and Gerbasi (24) (1933) have expressed the opinion that this increase in spleen size by reducing the blood volume and thereby the net capillary pressure may give rise to the inflow of lymph into the blood stream with dilution of the plasma. Searles and Essex (25) (1936) report 21 per cent. reduction in the cell volume and hemoglobin concentration after amytal and 19.7 per cent. in the red cell count. The other barbiturates insofar as they have been studied yield results indicating a movement of water in a similar direction. For example J. J.

Moher (38) (1937) found the plasma of cats diluted by barbital and nembutal as well as amytal.

In our own studies of amytal on rabbits we have inquired further into the sources of water coming into the blood. In two litters of rabbits, the entire animal was skinned and ground up except for the head and terminal portions of the extremities. The total water and partition into intra- and extracellular water of this rabbit "hash" is illustrated in Fig. 4. In the first litter an increase is seen in total water under amytal (one rabbit) and also in extracellular water, as contrasted with intracellular water. In the second litter (3 amytal animals contrasting with two normal animals) no significant change is seen in total water whereas amytal again obviously increased the extracellular water at the expense of the water within the cell. It appears obvious from these two experiments that the cells themselves release water under the influence of amytal. We shall return to the significance of this later on. According to Seeley, Essex and Mann (26) (1936), the admission of fluid into the blood stream may be of considerable importance as a preventive measure against shock when barbiturates are used for premedication, which use of amytal, as they have shown, tends to prevent the increase in blood concentration due to ether. This is reminiscent of the preventive effect shown by Burne (27) (1926) for morphine. Winter and I have seen the same after codeine in dogs.

So far as is known, the liver exhibits some increase in total water content under the influence of ether. We have examined this question with amytal and attempted to partition the water of the liver between the cells and the interstitial spaces, aware, however, of the uncertainty of the chloride method because some chloride is said to enter the liver cells. With this reservation, we may conclude that the data from the three oldest litters in Fig. 5, containing eleven rabbits altogether, indicate the movement of water from the interior to the exterior of the liver cells. The data from the youngest litter (on the left) indicate an opposite result, but these were the animals believed to be emerging from the anesthetic. The total water in all five litters was increased under the influence of amytal and this quite markedly in the larger animals.

For ether anesthesia no marked changes in intra- and extracellular water were found by McAllister (28) (1938). The determinations of the medulla water/cerebrum water ratio which is quite indirect suggest for both ether and morphine the same decrease of the cortex as found for amytal.

Whether or not the intracellular water of the body as a whole will be found significantly reduced with these two anesthetics is not to be predicted from the blood findings. On the other hand reduction of cellular activity in general appears to be associated with release of water from the cells. We have mentioned above that the cells tend to absorb water during increased muscular activity; for example I have

seen this in many cats exposed to cold environments. Here the intracellular water is regularly increased, but the increase does not depend entirely on shivering, and we have been inclined to explain it as part of a sympathetic response. Increase in intracellular water, it may be mentioned, when due to activity in cells, is ascribed to the accumulation of a larger osmotic pressure within the cell as a result of the metabolites produced. Stone's findings (29) (1938, 1940) showing decrease of

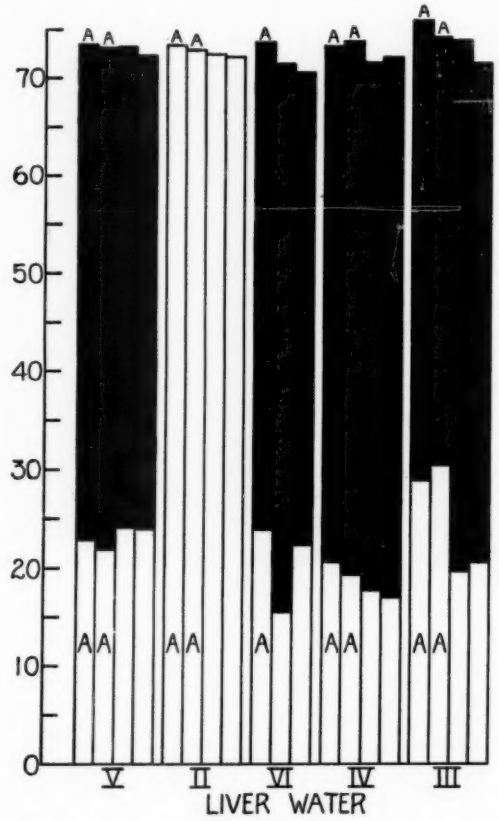

FIG. 5. Water of Rabbit Livers. Same arrangements as in Fig. 3.

lactic acid and phosphate after barbiturates accord with this conception by presenting the picture in reverse.

The hydrogen ion concentration of the cortex, according to Nims, McCulloch and Dusser de Barenne (30) (1939) is reduced in proportion to the depth of ether anesthesia, a typical pH finding being 7.1. Professor Nims tells me that in cats this amounts to 7.1 after morphine, and to 7.25 after amytal, which might speak for a greater depression

of cortical activity, but on the other hand electrocorticograms show the greatest depression of activity with ether, less with morphine, and the least with amytal. A point of much interest concerns the respective effects of ether and amytal upon the cortical vessels as opposed to the vessels of the hypothalamus. Ether relaxes the cortical vessels without affecting the hypothalamic vessels in monkeys whereas the reverse is true of amytal (Kennard (31), 1940). This latter dilation in the hypothalamus may be a factor of no little importance in determining the dilution of the blood resulting from the barbiturates, for vasodilation by bringing extra heat to this part of the brain (and, in fact, to the particularly vascular anterior hypothalamus) promotes the entrance of fluid into the blood (Barbour and Aydelotte (32), 1933).

Some reference should be made now to the capacity of anesthetics to promote the production of edema and also to their effect upon excretion of water by the kidney. In frogs, Neild and Serritella (33) (1934) have shown that after frogs immersed in water have come to weight equilibrium, exposure to anesthetics caused marked water absorption. This is greatest under chloroform, less for ether, still less for nitrous oxide and least for ethylene. This is of interest in connection with the older experiments of Magnus (34) (1898) who injected large infusions of sodium chloride into rabbits without producing edema; however, under chloroform, ether or chloral hydrate edema appeared. Ether and other anesthetics have long been known to produce oliguria and even anuria, and it is well-known that many anesthetics interfere with the excretion of phenolsulfonephthalein. The claim which Bourne and I made for increased blood concentration as a cause of urinary suppression by ether has never been disproven. The classical studies of MacNider (35) (1935) on the kidney showing that such factors as loss of alkalies and also old age in dogs interfere with urinary secretion under anesthesia are too well known to be discussed in detail here.

Very little information is available concerning the movements of water under the influence of gas anesthetics. Cyclopropane usually induces relatively few physiological changes of any sort, and while there is temporary depression of kidney function, this becomes compensated within a few hours (Waters and Schmidt (36), 1934). No influence upon the amount of water in the blood has been demonstrated.

The effect of anesthetics upon the heat regulating processes of the body are of some importance and are in part associated, of course, with water movement. The case of ether was mentioned above where anesthesia was shown to make dogs poikilothermous and to remove the water responses to cold. It has been shown in the Yale Laboratory of Pharmacology that the water responses to cold are reflected both in the serum specific gravity and the osmotic pressure. In response to cold the osmotic pressure increased, which in itself is a strong indication of an increase in intracellular water insofar as the specific gravity increase which occurs simultaneously is of the same order. Where the

serum specific gravity increase differs widely from that of the osmotic pressure the movement of lymph into or out of the capillaries should account for the difference. In the case of large doses of barbiturates in cats exposed to cold baths, Gilman and Barbour (37) (1940) have shown the interruption of these reflexes and sometimes their reversal. The same can be shown for large doses of chloralose, and smaller doses of this drug quiet the animal by cortical depression without either making it poikilothermous or disturbing the water shifting reflex.

Concerning the third category of the effect of anesthetic drugs upon the water movement in the body, namely water movement associated with the fate of the drugs, very little is known. We are at present examining some of the barbiturates with regard to the water content of the liver to see whether those which are not destroyed in the body may produce as great a change in the water content of the liver as that observed after amytal.

In summary, it may be said that for the anesthesia of mammals convincing evidence is now available that the cells of the cerebral cortex become dehydrated during the process. The blood becomes concentrated under ether but this largely, if not entirely, is due to the behavior of the spleen. There is evidence that the blood becomes concentrated under the influence of morphine as well as under the influence of morphine withdrawal, in which connection edema of the brain apparently occurs. Amytal and so far as is known, other barbiturates, cause marked decrease in the concentration of blood, with the addition of much water to the plasma. This is associated with some taking up of red blood cells by the spleen. The source of the additional water appears to be largely intracellular, the liver appears to take part in the release of cell water as well as the central nervous system, but itself as a whole becomes wetter under the influence of barbiturates. The gas anesthetics have never been shown to produce any profound shifts of water within the body. The effects of other groups of depressant drugs such as paraldehyde and the alcohols invite further attention. Third stage anesthesia, no matter how produced, is undoutedly associated with large loss of heat regulatory power, so that patients tend to become either under-cooled or over-heated depending upon the environmental conditions. With these changes are associated breakdown of the reflexes involving water movement in response to body temperature.

The above fragments of knowledge, or supposed knowledge, about anesthetic drugs suggest for the future many alluring problems of practical as well as theoretical importance.

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A combined meeting of the Section on Anesthesia of the Connecticut State Medical Society and the American Society of Anesthetists, Inc., will be held in conjunction with the Clinical Congress in New Haven, Connecticut, on September 17, 1940, at 8:00 P.M.

The program will be:

(1) "Anesthesia for Operations About the Head" by Lloyd H. Mousel, M.D., Mayo Clinic, Rochester, Minnesota.

(2) "Pentothal Sodium in Relation to Urologic Procedures" by Frederick Wilcox, M.D., Brooklyn Hospital, Brooklyn, New York.

(3) "Circulatory Effects from Traumatic Reflexes Stimulated During Abdominal Surgery" by E. A. Rovenstine, M.D., Bellevue Hospital, New York, New York.

"BRONCHOPNEUMONIA": THE ANESTHETIST'S RESPONSIBILITY? *

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A RELATIONSHIP between the treatment of pain and respiratory morbidity has long been recognized. It was expressed in the phrases "ether pneumonia," "postoperative pneumonia" and "postanesthetic pneumonia." In the light of present knowledge, it would be as logical to speak of "morphine pneumonia," "barbiturate pneumonia," "post-head-injury pneumonia" or "post-depression pneumonia." Realizing the non-specificity of the condition, the internist and the pathologist have come to write "Bronchopneumonia" in the records as a part of the clinical picture in nearly all illnesses following injury and surgery. The term is seldom missing from the terminal clinical record or autopsy report.

Two schools of thought have grown up to explain the appearance of pulmonary morbidity in patients subjected to surgery and injury. The first utilizes embolism as the blanket etiologic factor. Such a concept offers little encouragement that prevention can be accomplished other than through improvements in surgical technique and circulatory stimulation. The second explanation is based upon the belief that bronchial obstruction and alveolar inactivity is followed by absorption of the atmosphere in the affected area of lung, and bacterial growth follows in the resulting atelectatic air spaces. The latter concept serves as a rational basis for prophylaxis and treatment. Since atelectasis, massive collapse, and bronchopneumonia not infrequently follow the efforts of the anesthetist, he is interested in any analysis that can be brought to bear upon the subject which promises a reduction in the incidence and the mortality. If either drug administration or the care of drugged patients can be shown to affect the occurrence of pulmonary morbidity, consideration of the anesthetist's care of his patients may point the way to a reduction in such morbidity.

Efforts at the Wisconsin General Hospital during the past thirteen years have undoubtedly decreased the incidence of respiratory disease. The Department of Anesthesia was initiated in February, 1927. During the first six months of that year, the Department of Pathology reported six autopsies performed on patients who had died of "postanesthetic bronchopneumonia" on one surgical ward of sixty beds. Adequate records were not available at that time to make a statistical report covering the whole surgical service. The records of these six

* From the Department of Anesthesia, Medical School, University of Wisconsin.

cases contained notes of fever, rales, etc., being present before operation in four cases. The anesthetic drugs and techniques used covered the range of the available armamentarium at that time, including one minor infiltration by the surgeon. It was obvious that factors other than anesthetic drugs or techniques were etiological considerations. A strict ruling by the chief of surgery that patients must enter the hospital at least twenty-four hours previous to operation, that elective operations should not be performed upon patients with fever, acute upper respiratory disease, or abnormal chest findings, was a step in advance. Discontinuance of the custom of returning seriously ill patients from the operating rooms to large crowded wards, filled mainly with convalescent patients and visitors, was another valuable change.

MAJOR POSTOPERATIVE RESPIRATORY COMPLICATIONS

	1933	1934	1935	1936	1937	1938	1939	Total	Incidence
Bron. and hypo. pneumon.	33	18	44	35	27	21	42	223	0.752%
Lobar pneumonia	1	2	1	3	3	1	2	13	0.044%
Tuberculous pneumon.	1	1	0	1	1	1	4	9	0.030%
Partial atelectasis	15	7	17	20	27	24	33	143	0.482%
Massive collapse	7	6	5	8	10	2	4	42	0.142%
Lung abscess	0	0	0	0	0	1	0	1	0.003%
Empyema	0	0	0	0	0	1	1	2	0.007%
Others	0	0	0	0	0	0	4	4	0.013%
Total complications	60	34	67	67	68	51	90	437	
Total operations	3764	4064	4248	4167	4160	4461	4784	29648	
Incidence by years	1.59%	0.84%	1.58%	1.61%	1.65%	1.15%	1.81%	1.473%	1.473%

Note: Chest surgery excluded. Table shows actual number of cases.

A more efficient system of record keeping has developed since 1927. It has permitted analysis of our results in such a manner as to afford data on which to base changes in the manner and dosage of drug administration and anesthetic technique as well as data upon which to base changes in the nursing and professional supervision of patients depressed by pain relieving drugs and by injury, illness or surgical trauma. The incidence in recent years of major pulmonary morbidity and mortality is shown in the accompanying tables. It will be seen that the mortality among patients who acquire such major complications as atelectasis, massive collapse or bronchopneumonia after operations is one in four. Obviously, improvement lies along the line of prevention of major complications, not in treatment of bronchopneumonia after it is established. Perhaps it would be profitable to review the attitudes and procedures which, we believe, have tended to reduce the incidence of pulmonary complications and possibly have aided in the treatment of them. Such a review may offer food for thought to other groups, while at the same time aid us to see how we may further decrease our mistakes. An attempt to reduce to a common denominator the etiologic

factors involved in the production of pulmonary complications and thus indicate the direction which prophylactic measures might take, has led to the conclusion that, with rare exceptions, such morbidity *follows a period of interference with the normal functions of the respiratory mechanism whether due to drug action, trauma or illness.*

POSTOPERATIVE RESPIRATORY MORTALITY

	1933	1934	1935	1936	1937	1938	1939	Total
Deaths.....	27	15	20	8	7	11	26	114
Operations....	3764	4064	4248	4167	4160	4461	4784	29648
Incidence.....	0.72%	0.37%	0.47%	0.19%	0.17%	0.25%	0.54%	0.38%

Note: Chest surgery excluded. Table shows actual number of cases.

Many of the signs and symptoms seen in patients depressed by illness or trauma are also observed as side effects of drugs administered to relieve pain. Likewise the treatment of pain is most frequently necessary in this group of patients; therefore a summation of drug effects and the accompaniments of illness and trauma is not infrequently encountered. The clinical anesthetist may say, "What you are driving at is simply the necessity of avoiding oxygen want and carbon dioxide excess. Why all the palaver? Prevent respiratory obstruction and avoid or treat respiratory depression, and no harm can come to your patients." Right! But an understanding of the many ways in which obstruction and depression can be brought about may be an aid toward recognizing the best methods of avoiding and treating them. Illness, injury and pain therapy may interfere with normal function of the breathing mechanism through interference with normal (1) innervation, (2) psychic activity, (3) muscle tone, (4) activity of the respiratory center, and (5) inhaled atmospheres.

(1) The *Nerve Supply* responsible for breathing consists of (*a*) the *phrenic and intercostal nerves.* Partial or complete paralysis from drug action, illness or injury demands specific management. The acute circumstance of temporary intercostal paralysis from ether in the operating room is frequently corrected by the anesthetist through decreasing the depth of anesthesia or amplification of inspiration by manual pressure on the breathing bag. Paralysis of innervation over long periods deserves attention.

A woman with a cervical injury to the spinal cord, paralyzing the musculature below the 7th cervical segment, recovered from a major pulmonary complication, by frequent negative pressure clearance of secretions from the tracheobronchial tree through a tracheotomy opening made solely for that purpose, in the absence of effectual cough.

A boy, completely paralyzed below the second cervical segment with poliomyelitis, has been kept in an artificial respirator for 2 years. Careful nursing management to avoid contamination of the larynx and trachea has prevented pulmonary disease.

(*b*) The *reflex mechanism* governing normal breathing, coughing, swallowing and vomiting is most intricate. It involves cyclical, perfectly timed activation and inhibition of each component reflex with nicely coordinated, alternating muscular activity and relaxation. Illness (e.g., intestinal obstruction) and injury (e.g., following skull fracture and brain surgery) cause an imbalance of this mechanism in such a manner as to obstruct the airway or to permit contamination of the air spaces with foreign material. We anesthetists are all too familiar with hyperactivity of the laryngeal reflex. Do we always bear in mind the hyperactive oculo-cardiac, tracheo-cardiac and carotid sinus reflexes, or the possibility of a hypoactive laryngeal reflex in conjunction with a hyperactive vomiting reflex or the opening of an abscess or a blood vessel in the upper respiratory passages?

A woman whose oculo-cardiac and carotid sinus reflexes were normal during ward examination showed such marked hyperactivity during second plane ether or cyclopropane anesthesia that pressure over the eyeballs or the carotid sinus resulted in a complete cardiac standstill. Illustrating the reverse effect, a man, on whom asystole could be produced by eyeball pressure during ward examination, had a completely normal oculo-cardiac reflex while he was anesthetized with ether for a hernia repair.

A woman anesthetized for cholecystectomy with spinal block and previous sedative medication regurgitated gastric contents and inhaled a small amount into the trachea. The occurrence was followed by a brief period of respiratory and, what appeared to be, cardiac arrest. Prompt inflation of the lungs a few times with oxygen restored respiratory and circulatory conditions to their previous state. The quantity of aspirated fluid was not sufficient to cause noisy breathing or other evidence of tracheal contamination and must have exerted its effect through irritation of the tracheal mucosa. The experimental injection of a small quantity of dilute hydrochloric acid into a dog's trachea caused a marked drop in blood pressure and disturbed respiratory rhythm.

During the drainage of a lung abscess, it was accidentally ruptured into a bronchus and the air passages flooded with pus. Instantaneous utilization of gravity drainage (head low), prompt intubation and cleansing of the tracheobronchial tree with suction through the tube, rapid restoration of cough reflex, meanwhile rolling the patient from side to side, followed by intelligent nursing management prevented an exacerbation of the pulmonary disease.

Similar or less drastic measures are indicated when opiates, barbiturates, tribromethanol, or anesthetic gases and vapors produce depression of the cough reflex and ciliary activity. Excessive secretions, thick and tenacious from various drug effects, are difficult for the patient to remove, even when action of cilia and cough are normal. Not infrequently aspiration of mucus from the tracheobronchial tree under local anesthesia, in cases subject to continued pain or sedative therapy, is life saving. Such a procedure should be instituted promptly, and not reserved solely as a treatment for atelectasis or pneumonia.

A woman suffered multiple fractures and six weeks' hospitalization, with need for prolonged administration of narcotics and hypnotics. She entered the psy-

chiatric service uncooperative and "crazy." To keep her in bed the night of her arrival she was made to drink four drams of paraldehyde. Next morning she was in extremis with noisy, ineffectual breathing, resulting in acute oxygen want. A thorough tracheobronchial toilet with interspersed oxygen inflation of the lungs, followed by a "stir-up regime" every hour and oxygen therapy, permitted recovery. A cumulative effect of sedative drugs had disturbed the reflex protection of the larynx as well as the psychic poise of the patient. Some of the paraldehyde solution was aspirated. In a busy ward, this accident was not noticed until hours later.

A man of 36 years came to the hospital for appendectomy six weeks after recovery from pneumonia at the time of the rupture of his appendix. Appendectomy was performed under open drop ether. For the following 30 hours, pain alone (treated with morphine) disturbed his normal recovery.

36 hrs. postop. T. 100.2°, P. 88, R. 24.
41 " " T. 101. °, P. 120, R. 24.
44 " " T. 101.8°, P. 132, R. 26. Pneumonia, right side, diagnosed.
48 " " T. 103. °, P. 148, R. 40. Senior house staff called.
50 " " X-ray diagnosis of massive collapse.
52½ " " Bronchoscopic aspiration of tracheobronchial tree.
53 " " T. 101.6°, P. 96, R. 24, following which hourly change of position, deep breathing and forced cough were instituted.

Temperature, pulse and respiration normal the next day. Satisfactory recovery. How much better to have treated this man immediately following operation with the "stir-up regime". Certainly the temperature, pulse and respiration record at 36 hours demanded aid in clearing the air passages of excessive secretions which were dried from the effect of morphine and difficult to expel because of depressed ciliary and cough action.

(2) *Deviation From Normal Psychic Activity* not infrequently leads to gross obstruction of the respiratory passages and their contamination with nasal secretions, vomitus, etc. Patients psychically stimulated have been seen to refuse to turn the head or to expectorate when vomitus was in the pharynx. Psychic depression may also lead to disaster.

A patient with a papilloma of the larynx, somnolent from the hypodermic administration of an eighth of a grain of morphine, turned to the left lateral position (a position recognized by her and by her family as impossible for her during normal sleep). The attendant did not enter the patient's room for a period of a half hour at which time she was found dead from complete respiratory obstruction.

(3) *Muscle Tone:* Respiratory obstruction secondary to the excessive muscle tone produced by acute extreme oxygen want or carbon dioxide excess is familiar to every anesthetist and is properly treated. The obstruction resulting from a relaxed tongue partially covering the glottic opening when the patient is in the dorsal position varies in severity from unpleasant snoring and mild oxygen lack to complete obstruction and death.

A woman of sixty was anesthetized with ether and intubated in preparation for a gasserian ganglion operation. She recovered laryngeal reflex activity at the end of operation and coughed. The laryngeal tube was removed and an orderly was permitted to transport her, without a pharyngeal airway, to her room. Muscle relaxation was still present when she was placed in bed in the dorsal position without care as to the relative position of the head to the trunk or the mandible to the cranium. A few minutes later, she was pronounced dead by an ill-trained house surgeon and her family physician. Insertion of a pharyngeal airway and mouth to mouth inflation of her lungs until oxygen and a mask and bag could be secured, restored her and she walked out of the hospital in four days.

(4) The *Respiratory Center:* We all recognize that opiates, barbiturates and other sedatives and narcotics including gases and vapors decrease the sensitivity of the respiratory center to a normal stimulus and hence reduce pulmonary ventilation. Two unphysiologic practices have become common in the management of patients in respiratory depression. One is the administration of high tension oxygen (a very desirable therapeutic maneuver) with the neglect of the carbon dioxide factor. Because oxygen restores the appearance of the patient to normal, the remainder of the picture, high carbon dioxide, is forgotten. If depression of respiration is extreme, artificial aid to pulmonary ventilation is often indicated although a pink color can be maintained with oxygen therapy.

A man, having undergone thyroidectomy under inhalation anesthesia, became very restless after operation. To keep him in bed, a fortieth of a grain of apomorphine was ordered and four-tenths of a grain was given. Artificial respiration, manual at first followed by the use of a mechanical respirator for a few hours until the drug was detoxified, plus oxygen therapy, left him little the worse for the experience.

The other reprehensible practice is to administer oxygen-carbon dioxide mixtures over long periods of time to patients whose respiratory centers are depressed by drug action or injury. Such centers may be insensitive to or depressed by the carbon dioxide tension chosen. Carbon dioxide administration serves no useful purpose other than the production of hyperpnea. Where respiratory exchange is depressed other than temporarily, there exists a marked accumulation of carbon dioxide in the blood and tissues. Addition of carbon dioxide to the inspired atmosphere may further depress the breathing as well as further tax the patient's reserves of available base which can combine with the excess carbon dioxide.

A baby born with opiates and barbiturates, received from his mother during delivery, was given a mixture of 5 per cent. carbon dioxide and 95 per cent. oxygen, blown into his semi-closed bassinet, over a period of hours. He had a gasping, slow, jerky, and ineffectual type of breathing and was manifestly about to die. The mixture was discontinued and the bassinet flushed out with pure oxygen and kept well ventilated by that means. In a half hour, this baby's condition was restored to normal.

Depressed respiratory exchange caused by too liberal premedication is often enhanced by the effect of high concentrations of ether or cyclopropane. To combat such depression, carbon dioxide is often added to the respired atmosphere, either from a cylinder or by means of rebreathing. This technic increases the depth of breathing but is not physiologically sound. It is more logical to augment each inspiratory effort with manual pressure on the breathing bag as long as the depressive concentration of the agent must be maintained.

(5) *Modifications of Inhaled Atmospheres:* The effects of irritants are obvious and need not be mentioned here. Atmospheres containing subnormal tensions of oxygen may, if slowly produced, increase respiratory rate and possibly depth. However, when the reduction of oxygen tension is marked, depression of the respiratory center takes place. No stimulant drug, even carbon dioxide, will have the slightest effect on a respiratory center depressed by severe oxygen lack, until oxygen is restored.

A high concentration of carbon dioxide (30 per cent.) in oxygen was administered to a dog. Having produced a condition simulating anesthesia, the carbon dioxide concentration was increased and the oxygen tension correspondingly decreased through a period of convulsions followed later by respiratory depression and eventually respiratory arrest. Sodium cyanide was administered intravenously in adequate dosage but no respiratory activity took place until the lungs were ventilated with pure oxygen, when respiration was immediately resumed. The respiratory center remains inactive, regardless of the stimulus, until oxygen is restored. Excess carbon dioxide is a respiratory depressant.

It has been shown that gases differ in the rate at which they are absorbed from lobes or lobules fed by an obstructed bronchus or bronchiole. It may also be observed that the resulting atelectasis becomes complete (liver-like) more rapidly when oxygen or nitrous oxide is obstructed in a closed portion of lung than when nitrogen is similarly treated. For this reason, it is not desirable to leave the alveolar spaces filled with a readily absorbable gas at the end of anesthesia if depressed exchange or obstructed air passages are anticipated.

A woman was anesthetized with nitrous oxide-oxygen-ether atmosphere, intubated and the tube passed into the right bronchus, blocking the left bronchus. In one-half hour, an x-ray film showed the left lung to be completely atelectatic. The tube was withdrawn two inches, plane of anesthesia decreased, the bag distended and cough stimulated. The massive collapse had disappeared in a period of five minutes. Had the relief of obstruction been delayed a few hours, the cure would not have been so dramatic. "Bronchopneumonia" might have been the diagnosis. Bacteria grow readily in inactive alveoli.

The normal transport of oxygen and carbon dioxide in blood and tissues is dependent upon a certain biochemical balance which must undergo a shift to accommodate excess tensions of oxygen and carbon dioxide. Such shifts must be reversed to normal when room atmosphere is restored. If there is no special indication to the contrary,

anesthetic atmospheres should contain tensions of oxygen and nitrogen as nearly normal as is consistent with adequate oxygenation. Patients in biochemical imbalance tolerate badly sudden changes in oxygen and carbon dioxide tensions.

A woman of 45 years was given ten grains of barbital at bedtime and a quarter of a grain of morphine and one-hundredth of a grain of scopolamine at 8 the next morning. She was anesthetized from 9:30 until 11:30 with an ether-oxygen atmosphere by the carbon dioxide absorption technic for a complete perineal repair. A large face mask permitted 300 cc. of dead space (rebreathing) between the face and soda lime. Respirations were slow and shallow. Obviously under such conditions, the blood and tissues contained a tension of both oxygen and carbon dioxide much higher than normal. Blood pressure and pulse rate were normal throughout the operation. When the operation was finished, the mask was removed and the patient sent to the ward in good condition. One-half hour later, the ward attendant reported that the patient was in "shock." The systolic blood pressure was 60 mm. mercury, the diastolic 35, and the pulse rate 80. The skin was pale, but the patient was conscious without the anxious look of a shocked patient. Without therapy directed at the circulatory system, a perfectly normal circulatory condition had been restored 3 hours later. We interpret such a circumstance as a reaction to the *sudden* change in gas tensions of the respired atmosphere of a depressed patient. An atmosphere consisting of air with an adequate addition of oxygen only, would have been a better vehicle for the ether vapor. Less premedication would have permitted more adequate ventilation. A smaller mask would have reduced the amount of rebreathing. By these means, there would have been a more normal oxygen and carbon dioxide tension in the tissues during anesthesia, requiring less biochemical adjustment. Perhaps in any case a gradual dilution, by ventilation of the breathing bag and mask with room air for the terminal minutes of anesthesia, would have prevented the "pseudo-shock" with slow pulse seen in this patient.

Discussion

Try as we may, we have so far failed to prevent the occasional occurrence before, during and following anesthesia, of a period of interference with the normal functions of the respiratory mechanism. We still encounter patients after operation, after sedative and narcotic drug administration, after head injuries or even during debilitating illness who have atelectasis, massive collapse, bronchopneumonia and other major respiratory disease. What are we doing about it? Delay in the care of abnormally functioning respiration is fatal. Changes in pulse rate, respiration, blood pressures and body temperature afford earlier evidence of the onset of trouble than do physical signs such as cyanosis and auscultatory or percussion evidence. Such changes, however, can be masked by oxygen therapy. Careful inspection of the respiratory movements viewed from the foot of the bed, laterally and from the head may make evident the asymmetery which is the cardinal sign of atelectasis.

Similar plans of management have been found useful for prophylaxis and therapy. All patients markedly depressed from any cause

should be treated by what has been called the "stir-up regime." This means the hourly insistence upon meticulous attention to three details. The attendant must conscientiously attempt to make the patient (1) take several deep breaths; (2) cough effectively, and (3) change his position radically. Active aid and encouragement by the attendant is required. It is surprising how frequently a depressed patient with inactive breathing and inefficient or absent cough, can be made to expel large quantities of secretion from the air passages. The unconscious or completely uncooperative patient may be made to take several deep breaths by pouring pure carbon dioxide, as one would pour water, from a rubber tube held over the face. Such a flow of gas added to the inspired air may force the desired ventilation of inactive alveoli. For this specific purpose, rarely otherwise, do we find carbon dioxide of therapeutic value.

Where there is the slightest evidence of obstruction or of atelectasis, we have come to feel that the tracheobronchial toilet, described elsewhere, is justified. We feel confident that this apparently drastic regime, when instituted early and faithfully carried out, has reduced the incidence of major respiratory complications in our hospital and has reduced the severity of many of those which we still encounter. Focusing the attention of the house staff upon the extraneous pharmacologic effects of pain-relieving drugs has aided in our efforts to avoid the injudicious use of sedatives and to promote individualization of dosage of such agents.

CONCLUSIONS

It is our opinion that a period of interference with the normal functions of the respiratory mechanism precedes atelectasis and bronchopneumonia, and that it is one of the anesthetist's functions to try to prevent or at least minimize such periods of interference.

Careful selection of drugs and combinations of drugs for pain relief, and individualization of their dosage, further this aim.

Prompt and efficient application of means for the correction of the abnormally functioning respiratory mechanism is essential.

1. Obstructed airways must promptly be made patent.
2. Oxygen therapy must be utilized early.
3. Markedly depressed breathing must be made adequate either manually or mechanically. (Carbon dioxide therapy is not a physiologic remedy for depressed breathing. Oxygen therapy is logical for one-half the picture only, and may require supplemental augmentation of respiratory exchange to restore normal conditions.)
4. The "stir-up regime" and "tracheobronchial toilet" are valuable both prophylactically and therapeutically for many depressed patients.

INTRAVENOUS ANESTHESIA *

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THE history of intravenous anesthesia is interesting (1). In sixty-two of the sixty-eight years elapsing since Ore of France first used chloral hydrate to produce intravenous anesthesia, the success of the method was not sufficiently marked to impress medical practitioners that the method had come to stay. One of us (Adams) is presenting the story of intravenous anesthesia in a monograph (2). We have been convinced, since early in 1934, of the efficacy of the method. There are some reasons, aside from scientific ones, which will make intravenous anesthesia a permanent technic. A surgeon who wishes to utilize the appeal for intravenous anesthesia that patients have for it, can increase his surgical practice on this basis. Induction of anesthesia by intravenous methods is pleasant and patients prefer it as compared to local and inhalation anesthesias. On the other hand, surgeons who employ rectal anesthesia are less likely to feel the need for intravenous anesthetic agents except in instances in which the longer lasting effect of rectal anesthesia is undesirable.

GENERAL CONSIDERATIONS

For the professional anesthetist there is a very great appeal in the use of intravenous anesthesia, for he can employ it to advantage many times not only alone but also in connection with many other agents and methods. The usefulness of such combinations becomes increasingly apparent as time passes. Not only is the scope of intravenous anesthesia thereby increased, but the risk of overdose may be lessened, since, usually, smaller total doses of intravenous agents are required than is true of other agents.

It has seemed to us that it might be interesting briefly to summarize some of our experiences during the period from June, 1934 to January 1, 1940 (3). During this period pentothal sodium was used by us in more than 16,500 operations. This drug (chemically the sodium salt of ethyl 1-methyl butyl thiobarbituric acid or the thio-analogue of pentobarbital sodium) has, in a measure, fulfilled some of the requirements desirable in a good anesthetic agent for intravenous use. Among these characteristics may be mentioned comparative brevity of action together with sufficient potency to produce surgical

* Read before the meeting of the Academy of Medicine of Northern New Jersey, Newark, New Jersey, February 27, 1940.

anesthesia without causing severe or prolonged respiratory depression. Since one of us (Adams) has written a synopsis of all the chemical and pharmacologic data that have been published on the subject and since an extensive literature is readily available to anyone interested in pentothal sodium, we should like to confine our remarks largely to the clinical intravenous use of this drug, although with minor changes in what will be said, these remarks will apply equally well to evipal soluble. Since our experience has been principally with pentothal sodium, however, we shall confine our remarks to its use.

PRELIMINARY MEDICATION

For most patients it has been definitely advantageous to use preliminary medication, consisting of nembutal; for adults, 1½ grain (0.1 gm.) taken at bedtime the night before the operation and repeated forty-five minutes before the operation in the morning, plus the administration of morphine sulfate, ⅙ grain (0.01 gm.) and atropine sulfate, $\frac{1}{150}$ grain (0.00043 gm.) by hypodermic injection. As we have mentioned before, we believe that the use of atropine is advantageous in connection with pentothal sodium, and certainly morphine reduces the amount of pentothal sodium that it would otherwise be necessary to use. For the resistant individual adult patient, it is wise to administer morphine intravenously in additional small amounts if at the time of operation it is obvious that the dose of pentothal sodium used for the induction of anesthesia is larger than that for the average patient. The dose of morphine is usually ⅛ grain (0.008 gm.), ⅙ grain (0.01 gm.) or ¼ grain (0.016 gm.), administered very slowly. The anesthetist watches the patient's pupil and stops as soon as it becomes small. After the morphine has had a minute or two to exert its effect, the injection of pentothal may then be resumed and it will be usually observed that the patient who was previously resistant now responds to the ordinary doses of pentothal sodium.

DOSAGE

A solution of 2.5 per cent. pentothal sodium is the concentration which we use at The Mayo Clinic. We can say without fear of contradiction that it is the best one from the standpoint of the patient. It may not, of course, be convenient for the administrator and so the anesthetist must decide whether he will do the best thing for the patient or the convenient thing for himself. The reason for not using 5 or 10 per cent. solutions is that in an occasional case the physician will encounter delayed thrombophlebitis in instances in which the stronger solutions are used and this type of thrombophlebitis is definitely disabling to the patient for a number of weeks and is moreover very unpleasant. It may be inadvertently overlooked by those physicians who may not have the opportunity to follow up their patients during a period of several days and therefore fail to see untoward

results of this type. We have been unable to detect any material difference in the production of adequate surgical anesthesia when a 2.5 per cent. concentration is employed as compared to solutions of higher concentrations, provided doses of comparative size are employed. There is another factor which operates in favor of the use of a dilute solution which is of interest to those who are training new men in the technic of intravenous anesthesia: we feel that there is less danger of the beginner's administering an overdose to a susceptible individual if a 2.5 per cent. solution of pentothal sodium is employed than there would be if a more concentrated solution of the drug were used.

It is always safe to say that the solution should be freshly prepared; on the other hand, we have frequently used solutions that have been made up for twenty-four to thirty-six hours and they have seemed to be effective. If there is a reason for making the solution freshly, it is mainly that such a solution would be more potent than one which had been standing for a time. In a few cases we have thought that a solution that was twenty-four hours old was not so effective as a fresh solution; however, we could not be sure of it. If the solution is to be kept overnight for use on the following day, it seems advisable to exclude light and exposure to the air as much as possible. In the case of solutions kept in syringes for longer than a few hours, some precipitation may occur on that part of the plunger of the syringe at which the solution comes into contact with the air. Although this slight precipitation apparently has no untoward effect on the efficacy of the solution in the syringe, it may be sufficient to prevent free movement of the plunger in the barrel of the syringe. This may be prevented by slightly withdrawing the plunger and wiping off any accumulated precipitate with a sterile sponge, moistened with sterile water or alcohol.

There are, of course, many devices for the administration of the solution. Our preference is a 20 cc. eccentric Luer-lok syringe with a 1½ inch (about 4 cm.), short bevel needle. It is with such a device that the drug has been administered in this series, and although it may not be the most satisfactory device for other anesthetists, at least for us it has been.

TECHNIC OF ADMINISTRATION

We now come to that part of the technic which must be mastered if the method is to be used on all patients for whom its use may be indicated, and that part is the ease with which venipuncture should be carried out. There are certain fundamentals which have been called to our attention so often that we think it is worth while to emphasize them here. First, the anesthetist should examine the patient for available veins that are large enough to accommodate a 20 gauge needle. Such veins are most commonly to be found in the antecubital fossae of the arms or the saphenous magnus vein at a point anterior and proximal to the anterior tibial malleolus. The veins on the backs of the

hands and wrists are frequently used. There are a few patients, who because of obesity or for other reasons, do not present easily accessible veins. The method may still be used in such an event if heat is applied to the extremity to engorge the surrounding tissues with blood and if the tourniquet is applied rather close to the site of venipuncture. There should be little delay in doing venipuncture after the time that the heat has been removed. It must be obvious that if heat is used, then the antiseptic solution that is applied to the skin should be at least as warm as the arm to which it is being applied. In some patients pricking with the needle will cause the vein to disappear. In such cases it is probably advisable to raise a small wheal with a local anesthetic such as is commonly done in connection with venipuncture for transfusion of blood, or in connection with phlebotomy, wherein a large caliber needle is to be used. One very important procedure in connection with venipuncture is adequate, tight stretching of the vein at a short distance from the tourniquet so that it will not be displaced by the needle, but will be pierced by it. We should like to emphasize this point by saying that not infrequently, when one anesthetist finds venipuncture difficult, another will make it appear very easy by shortening the distance from the site of venipuncture to the point of application of the tourniquet to as little as 1 or 2 inches and that the successful anesthetist will definitely stretch the vein, whereas the unsuccessful one will not. The question of venipuncture must be given real consideration by those who wish to apply this method, because if venipuncture cannot be carried out, there is no opportunity whatever to use the intravenous method of anesthesia, and if venipuncture is awkwardly and painfully done, very few patients will care to undergo the procedure in order to utilize whatever benefits may be derived from use of the method. So far as the anesthetists are concerned, one anesthetist may be greatly preferred to another by various surgeons because one is more adept at venipuncture than the other. Certain other points in connection with the successful maintenance of venipuncture for long periods of time may be mentioned. If only infrequent injections are required for maintenance of anesthesia, clotting in the needle may occur. By keeping the syringe on a level which is higher than the point of the needle, back flow of blood into the needle and syringe is minimized. This, together with occasional injections of a few minims of solution, usually serves to prevent clotting within the lumen of the needle. When the condition of the patient is such that an intravenous infusion of physiologic salt solution is desirable throughout the course of the operation, it may be more convenient to inject the intravenous anesthetic solution into the infusion tubing. The most suitable situation for this is that part of the rubber tubing nearest the needle in the vein.

For the average adult the anesthetist may inject 4 to 5 cc. of a solution of 2.5 per cent. pentothal sodium in fifteen or thirty seconds,

although it is safer to take a longer time to complete the injection—one minute. For weak, debilitated and elderly patients, however, half this dose and twice this time should be employed. As soon as the injection is begun the patient should be asked to count or to raise an arm so that when unconsciousness occurs, it will be apparent to the anesthetist.

If the patient is to breathe air, a small square of paper the size of a postage stamp (one layer of cleansing tissue), attached to a thin strip of adhesive, should be arranged over the nostrils and the lips of the patient. The motion of this butterfly paper will indicate that respiratory exchange is taking place and it is a very satisfactory indicator as to the patency of the patient's airway. If oxygen or a mixture of nitrous-oxide and oxygen is to be administered simultaneously, the mask should be applied to the face as soon as the patient becomes unconscious. During maintenance of anesthesia, the anesthetist is guided largely by the depth of the respirations; that is, if the patient is overdosed the respirations will stop and if the patient is very lightly anesthetized, respirations will be increased in depth. Sometimes a patient will phonate or move an extremity, either of which, of course, indicates light anesthesia and requires that an additional 1 or 2 cc. of solution be injected. The most satisfactory way of administering the agent is to retain the needle in the vein and inject solution intermittently as it is needed, in principle similar to that of the use of ether by the semi-open drop method. Thus, it is difficult to say in advance what dose of pentothal sodium should be used for a given patient. Naturally, if the operation is long, more pentothal sodium will be needed than if the operation is short. Although the factor of preliminary medication enters into consideration for a very short minor operation, it is often not necessary to administer preliminary medication, but for major operations it is desirable. In deep anesthesia the eyeball does not move, whereas in light anesthesia it often does. The pupil is of no particular significance because, usually, before dilatation of the pupil caused by too deep anesthesia would occur, the patient's respirations already would have stopped and the patient's color would indicate hypoventilation. It is important that the chin of the patient be sustained to provide a free airway. For some very minor operations, it is sometimes possible to maintain the patient in a state of anesthesia so light that he may answer questions, but frequently the patient will complain of pain at the time of operation, but subsequently will have no memory of it. Nausea in many cases may be controlled by the use of a small dose of pentothal sodium.

CONTRAINDICATIONS

If we may assume that venipuncture is possible, we may then discuss the cases in which the method probably should not be used. There are certain circumstances that influence the anesthetist's decision in this matter. Among them are: (1) the circumstance that the patient

will breathe air during the period of anesthesia, (2) the circumstance that he may breathe oxygen during the period of anesthesia, (3) the circumstance that he may be breathing a mixture of nitrous oxide and oxygen during this period. It is advisable, we think, to mention these points in definite connection with contraindications rather than in a general way; for example, we do not advise the administration of pentothal sodium by this method to children less than ten years of age. We would be very emphatic about the point in case the child were to breathe air. We would be less emphatic if the child were to inhale oxygen and we should, as yet, even question the advisability of using this agent if the child were to receive a mixture of 50 per cent. nitrous-oxide and 50 per cent. oxygen. The point that we wish to make in this connection is that the child who is less than ten years old usually has small respiratory passages and that the anesthetic agent administered in anesthetic doses definitely will depress the child's respirations and take away from him his ability properly to ventilate himself. This we have observed more than once in instances in which a child has been breathing air. It is, of course, very much less noticeable if oxygen or nitrous-oxide and oxygen in 50 per cent. concentrations are being administered. For this same reason it seems clear that persons who have considerable respiratory obstruction should not be anesthetized by means of this method. Some operations for lesions about the upper respiratory passages represent such contraindications. Since the electrocautery is used so frequently in the treatment of these lesions, an arrangement which is free from the hazards of fire and explosion is also desirable. Therefore, although intravenous anesthesia may be contraindicated unless certain adjustments are made, by altering the physical arrangement in such a way that the patient's airway is under control, a contraindication is changed to an indication. This is accomplished by first anesthetizing the larynx before the patient goes to sleep. A solution of 10 per cent. cocaine or metycaine is suitable for this purpose; the patient's tongue is pulled forward and the region of the glottis is sprayed with the local anesthetic solution. Even more satisfactory anesthetization of the vocal cords can be obtained if the solution is instilled by means of a laryngeal syringe under indirect laryngoscopy. The patient is then anesthetized with pentothal sodium and an endotracheal tube is passed. The patient's airway is then assured and he may be permitted to breathe air, oxygen or a mixture of 50 per cent. oxygen and 50 per cent. nitrous-oxide, depending on the requirements of the particular case.

While considering the subject of anesthesia for operations on or about the upper respiratory passages, it may be stated that the combination of topical and intravenous anesthesia in the presence of a good airway is proving superior in most instances to methods we have previously employed. This includes bronchoscopic and esophagoscopic examinations for certain patients as well as certain operations on the

larynx and adjacent structures under direct laryngoscopy. It is not wise to use this combined method for patients who have cardiac decompensation plus dyspnea. It is particularly dangerous for those patients who for some time have not been able to lie down without suffering dyspnea. It is generally considered to be inadvisable to use pentothal sodium in anesthetic doses for individuals who have marked damage to the liver and kidneys. From our experience we cannot say that this is a very definite contraindication, because we have seen the drug used in patients whose liver was almost destroyed and they have, we think, with one exception, tolerated the drug as well as they might have tolerated any other anesthetic agent. Nevertheless, the anesthetist should be conservative in using the agent that we are discussing and probably not use it in the presence of these conditions.

There is the question of the advisability of using this agent or method in the presence of marked hypotension or in the presence of marked shock caused by severe hemorrhage. There is a question as to the advisability of using it in the presence of very severe anemia. Certainly, under such circumstances, oxygen should be administered simultaneously and in all probability it would be best to administer a mixture of nitrous-oxide, 50 per cent., and oxygen, 50 per cent.

Recently, it has been suggested that pentothal sodium should not be used for those patients who have been prepared for operation by sulfur compounds such as sulfanilamide. Probably a barbiturate should not be used when a drug such as sulfanilamide has been used in large doses, the administration of which has been continued up until the time of the operation (4). At first, some of us felt that evipal might be the agent of choice under such circumstances, but there has been a tendency to avoid the use of all barbiturates under such circumstances. If barbiturates are used, a minimal dose should be employed and the nitrous-oxide and oxygen mixture administered simultaneously, augmented, probably, by the use of local anesthetics also.

ORDINARY AND SPECIAL USES OF PENTOTHAL SODIUM

It probably is worth while at this point to mention some of the ordinary and special uses to which pentothal sodium has been put to advantage in our series. We have found it particularly useful for old persons; the reason probably is that very little anesthetic is required for such patients and that a mildly potent one such as pentothal sodium in very small doses is usually sufficient. There are certain uses to which the method may be put that enhances its value; for example, a small dose, 5 or 10 cc. of a solution of 2.5 per cent. of the drug, may be administered to induce anesthesia and it may then be maintained by the administration of any inhalation anesthetic. In the presence of hypertension this has been satisfactory, because the pentothal tends to do one of two things: (1) either it will lower the blood pressure during the period of induction with gas or ether or drop ether, or (2) it will

tend to prevent the marked elevation in blood pressure that often is to be observed when patients who have hypertension are anesthetized with a general anesthetic. In connection with local anesthesia, a small dose of pentothal sodium may be administered just before the block anesthesia is to be carried out; for example, a block for bunionectomy. All patients appreciate the relief afforded by the drug which permits them to avoid the pain associated with the injection of local anesthetics.

The method is very valuable in connection with spinal anesthesia when the anesthetic effect of spinal anesthesia is beginning to wear off and if the last part of the operation does not require relaxation so much as it does numbness. In those cases in which pentothal sodium is used in combination with spinal anesthesia, it is particularly advantageous to administer oxygen and nitrous-oxide, 50 per cent. each. The patient's breathing will be better and his respirations may be more readily observed, but the anesthetist must watch the patient's blood pressure and if it falls below 80 mm. of mercury, systolic, 25 mg. of ~~epinephrine~~ should be administered intravenously without delay. Similar combinations with other blocks, such as sacral, abdominal or brachial plexus, are used frequently to advantage. The method has one outstanding feature, which is that the combination is fireproof and nonexplosive, and not particularly difficult to carry out, nor is it very expensive.

CONCLUSIONS

For the anesthetist who has little choice of methods and who for the most part uses ether by the semi-open drop method for anesthetization, induction with pentothal sodium, using small quantities, is valuable because it may frequently be substituted for gas induction with ether maintenance. Large doses (0.5 gm. or more) of pentothal sodium should be avoided if the drug is to be followed by an inhalation anesthetic because respiration usually will be depressed too much to be satisfactory. The use of this agent and method for ambulatory patients is possible but is not as satisfactory as it is in instances in which the patient is hospitalized. The individual who has received even a small dose of pentothal sodium intravenously, should be treated as one who is inebriated and should not be allowed to go abroad alone until recovery. From our experience in this series of cases, we believe that it would be safe to say that the method has been generally satisfactory, provided that it is not used in cases in which it is contraindicated and provided it is administered by someone who will not overdose the patient.

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THE EFFECT OF VARIOUS TISSUES ON THE DETOXIFICATION OF EVIPAL IN THE DOG

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The ultra-short action of evipal-sodium (salt of cyclohexenylmethyl-N-methyl barbituric acid) [1] has interested many investigators in regard to the tissues concerned in its inactivation. The original contention of Weese (1) that evipal is destroyed by the liver has also been suggested by Cameron and deSaram (2). The conclusion was made essentially upon the prolongation of evipal action following preliminary injury to the liver by various agents. Since the decrease in function of the liver was not determined, its full significance was not evaluated in their studies or subsequent ones. Furthermore, except for the kidney (3), the role played by other tissues has not been investigated. An attempt was made in this study to establish more clearly the significance of the liver and other tissues in the destruction of evipal.

Procedure and Results

Adult dogs were used, three (3) having been prepared for blood pressure recording with a Van Leersum carotid loop. Evipal was administered intravenously in all cases at a rate of 4 cc. per minute, the narcotic dose being accepted as 30 mg. per kilogram (1). All solutions

TABLE 1

Effect of Optimum Concentration of Evipal (5%) Given Intravenously in Dogs

No. of Dogs	Deep Sigh	Maximum Variations During Anesthesia			During Depth of Anesthesia					
		Blood Pressure	Resp. Rate	Heart Rate	Lid Reflex	Wink Reflex	Response to Pain	Muscle Tone		Recovery
								Jaw	Skeletal	
	sec.	mm. Hg	min.	min.						min.
19	35 (20–50)	132/86 to 70/40 to 120/90	32 to 8 to 38	102 to 166 to 90	Markedly depressed or absent	Moderately depressed	Absent	Moderately decreased	Markedly decreased or absent	98 (53–170)

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[1] Acknowledgment is made of the generous supply of evipal sodium furnished by the Winthrop Chemical Co., Inc.

were freshly prepared. At approximately 5 minute intervals, records were made of various physiologic phenomena noted in Table 1. Pain was initiated by clamping the muco-cutaneous region of the anus. Recovery or end of anesthesia was regarded as the moment when the dogs showed normal reflexes and were able to support their body weight.

Control studies on 19 dogs were carried out to determine the optimal concentration of evipal following intravenous administration. The concentrations of evipal used were 2.5, 5 and 10 per cent. It was established from 43 observations that a 5 per cent. concentration of evipal gave consistent results with respect to the depth, duration and recovery of anesthesia and was therefore considered an optimal concentration. In Table 1, the results showing average responses with this concentration are briefly summarized. While the respirations decreased progressively in depth, there was an initial but temporary increase in minute volume followed by a fall. The blood pressure generally showed an acute and transient fall which was prevented (5 experiments) when a preliminary intramuscular injection of ephedrine sulphate (1.5 mg./kgm.) was given. While ephedrine did not delay the onset of anesthesia, it did shorten the duration. With the dosage used, the wink reflex was only moderately depressed but was exceptionally absent. Anesthesia appeared in about one minute after the injection and remained moderately uniform in depth for about 20–25 minutes. Recovery was noted at an average of 98 minutes.

Hepatic damage was induced by chloroform anesthesia of 1½–2 hours duration in 5 control dogs previously fasted for 16–18 hours. The extent of injury was determined 48 hours later by the bromsulphalein method (4) and compared to control values. The plasma dye retention after 30 minutes in dogs with liver damage ranged between 45–80 per cent.; the control values averaged 4.1 per cent. A full narcotic dose of evipal was given to 3 dogs and ½ of the dose to two others. Table 2 summarizes the results. The death of one dog and the mark-

TABLE 2

EFFECT OF EVIPAL IN DOGS WITH LIVER INJURY AND FOLLOWING EVISCERECTOMY

Condition of Dogs	No. of Dogs	Narcotic Doses of Evipal 30 mg./kgm.	Recovery	Remarks
Liver Injury by Chloroform	3	Full dose	min. (290),* 240, 390	*Died
	2	½ dose	172, 110	
Eviscerectomy	3	Full dose	(30),* (67),* (240)*	*All died
	2	½ dose	150, 203	Slight muscle tone
	1	⅓ dose	120 (177)*	*Died after 2nd injection

edly prolonged anesthesia in three others suggests the importance of the liver in the detoxification of evipal and confirms previous findings (1, 2).

Hepatic function, however, was not completely eliminated by the chloroform anesthesia and its significance therefore not fully revealed. Accordingly, in six other control dogs, the liver and most of the gastrointestinal tract were removed under light ether anesthesia (40–60 min.) (5). The animals were maintained for 6–17 hours with periodic intravenous injections of 10 per cent. glucose solution. Blood sugar determinations (6) were frequently made and ranged in value from 122–510 mg. per cent. Three to five hours after operation and apparent recovery noted by the dog's actions and ability to walk, evipal was administered in varying doses depending on the post-operative weight. The depth and duration of anesthesia were recorded.

TABLE 3

EFFECT ON DOGS OF EVIPAL SOLUTION AFTER INCUBATION WITH VARIOUS RAT TISSUES

No. of Observations	Tissue Used	Amt.	5% Evipal in Sal.	Time of Incub. 38° C.	During Depth of Anesthesia			Recovery	Approximate Destruction Evipal
					Lid Reflex	Wink Reflex	Skeletal Muscle Tone		
		gms. or cc.	cc.	min.				min.	%
9	Control	—	15	60	Markedly depressed or absent	Moderately depressed	Markedly depressed	109 (90–184)	—
16	Liver	9 (5–14)	21 (10–40)	30 (10–60)	Slightly depressed	Normal	Very slight decrease	36 (1–57)	66
12	Skeletal Muscle	11 (9–14)	25 (20–30)	30	Slightly depressed	Normal	Moderately decreased	57 (38–65)	48
8	Spleen	10 (7–14)	22 (15–30)	30	Moderately depressed	Normal	Moderately depressed	68 (46–80)	38
10	Kidney	8 (5–14)	22 (14–32)	45 (30–60)	Absent	Moderately depressed	Absent	96 (80–119)	0
6	Brain	2	10	30	Absent	Moderately depressed	Markedly depressed	116 (92–126)	0
6	Oxalated Dog Blood	20	1*	30	Absent	Markedly depressed	Absent	134 (79–192)	0

* 1 gram of crystals of Evipal Sodium.

It will be seen from Table 2 that the full narcotic dose of evipal is fatal in eviserectomized dogs and that death occurs much sooner than in those dogs with liver injury due to chloroform anesthesia. Dogs receiving one half the dose recovered with normal lid and wink reflexes and pain response, but with only a slight return of muscle tone. Two

injections of ⅓ of the dose were given to one dog. Full recovery was noted in 120 minutes after the first administration. Death followed in 77 minutes after the second. Control dogs receiving ½ or ⅓ of the narcotic dose recovered in about 51 and 28 minutes respectively.

The fact that eviscerectomized dogs, receiving subnarcotic doses of evipal, recovered would seem to indicate that other tissues than the liver played a part in the detoxification of evipal. To determine this, a series of in vitro experiments were performed. Freshly macerated tissues of the rat were put in evipal solution made up to 5 per cent with physiological saline and incubated at 38° C. for 10 to 60 minutes (average 30 minutes). Some difficulty was experienced in getting clear solutions of macerated liver and spleen. After centrifuging, the fluid was drawn off and administered intravenously to dogs at 4 cc./min. with a dose of evipal of 30 mg./kgm. Control injections were made with incubated 5 per cent. evipal solution in saline. The reactions and duration of anesthesia of each dog were noted.

Table 3 shows the average responses of dogs after injections of evipal previously incubated with various macerated rat tissues and oxalated dog blood. It would appear that liver, skeletal muscle and spleen exert a significant action in nullifying the depressant action of evipal. The magnitude of such effect is in the order of the tissues named. In the case of liver, the duration of narcosis was decreased 15 per cent. after 10 minutes' incubation, 66 per cent. after 30 minutes and 90–100 per cent. after 60 minutes. Dogs in the last group showed nausea, emesis, mild excitement but no narcosis. After incubation with macerated muscle or spleen for 30 minutes, evipal anesthesia was shortened about 48 and 38 per cent. respectively. No decrease of the time of anesthesia was noted with evipal solution incubated alone or with rat kidney, brain or whole dog's blood. The negative results obtained with macerated kidney and brain tissues appear to minimize the factor of dilution in these incubation experiments.

Discussion

In the preliminary phase of this study, attention is called to the fact that a 5 per cent. evipal solution is the optimal concentration for narcosis in dogs when given intravenously at the rate and dose used. The signs noted during the depth of anesthesia as well as the duration of anesthesia were significantly constant.

According to Weese (1), the minimal narcotic dose of evipal sodium (30 mgm./kgm.) given intravenously in dogs is approximately ⅓ of the minimal lethal dose (100 mg./kgm.). The data in this study indicates that the same narcotic dose produces an abnormally prolonged anesthesia in dogs with hepatic injury and death in maintained eviscerectomized animals. The liver thus plays a major role in the destruction of evipal. This contention is further brought out by the incubation studies.

However, the fact that eviscerectomized animals receiving 33 or 50 per cent. of the narcotic dose lived at all and showed normal or prolonged anesthesia followed by recovery suggests that other tissues may detoxify evipal or that it may be excreted rapidly. Such detoxification of evipal is also suggested by the incubation studies in which muscle and spleen shortened the narcotic action significantly. Hence, while the liver is the major site of detoxification, it is aided greatly by skeletal muscle and the spleen. The brain, kidney and blood apparently do not decrease evipal action.

Although the incubation experiments have shown that various tissues can destroy evipal sodium, no quantitative measure of such activity has been made in the living animal. The findings are therefore only qualitatively important. Furthermore, the actual mechanism involved in decreasing the action of evipal has not been revealed in these studies. The evipal may be adsorbed as such, conjugated in the various tissues, or excreted in small amounts in the urine unchanged (1).

CONCLUSIONS

Studies on eviscerectomized dogs and with incubated macerated tissues revealed more clearly the important role played by the liver in the inactivation of evipal. Skeletal muscle and spleen also shared in this action. Brain, kidney and blood had no effect on the destruction of evipal soluble.

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THE PRODUCTION OF VENTRICULAR TACHYCARDIA BY ADRENALIN IN CYCLOPROPANE ANESTHESIA *

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In a series of papers Levy (1–3) showed that chloroform sensitizes the heart of the cat to stimulation of various kinds so that ventricular tachycardia and fibrillation may result. Beattie, Brow and Long (4) confirmed Levy's work and in addition concluded from further experiments that within the hypothalamus lies a center, or centers, the removal of which abolishes extrasystoles of chloroform origin. Fibers pass from this region into the intermedio-lateral column of the grey matter of the cord, from which come preganglionic sympathetic fibers which synapse in the stellate and upper thoracic white chain ganglia; post-ganglionic fibers run to the heart. Allen (5) has indicated a similar efferent pathway for the trigemino-sympathetic impulses which cause premature systolic arrhythmias on insufflation of benzol by rabbits.

Recent studies have shown that cyclopropane resembles chloroform in rendering the heart so sensitive to adrenalin that various irregularities result from its injection. The fact that a dose of adrenalin of too low concentration to produce ventricular tachycardia in a normal unanesthetized dog will do so with great regularity in the same animal under cyclopropane anesthesia has been well established (6, 7). This paper is a study of some of the mechanisms involved.

Influence of Nerve Centers Above the Pons

To test the influence of any nerve center in the brain stem or higher on the cardiac response to adrenalin under cyclopropane, it was planned to make injections before and after decerebration. Dogs were used as the experimental animals because it has been our experience that conclusions from experiments with anesthetics on the dog may be applied to man with much more certainty than those from the cat.

In all experiments under cyclopropane anesthesia dogs were anesthetized with cyclopropane without premedication, intubated to insure an open airway, and connected through a soda-lime carbon dioxide absorber to a 100 liter bag containing a 33 per cent. mixture of cyclopropane in oxygen. This concentration of the anesthetic agent produces deep surgical anesthesia with at least partial intercostal paralysis in dogs. The animals were allowed to equilibrate on this constant mixture for at least 30 minutes before any injection was made.

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Fifteen dogs in deep surgical anesthesia were injected intravenously with adrenalin in concentrations of 0.003 to 0.012 mgm. per kilogram in 5 cc. of normal saline at a constant rate of 1 cc. per 10 seconds until ventricular tachycardia was observed in the electrocardiograph. In this way a control dose of adrenalin was determined which would bring on ventricular tachycardia for 30 seconds or more. Continuous electrocardiograms (Lead II) were taken throughout the period of irregularities. Under the same concentration of cyclopropane these dogs were then decerebrated by one of three methods.

On 11 of the dogs a modification of the anaemia method of Pollack and Davis was used (8). These decerebrations were done in two stages. In the first stage the dog was anesthetized with sodium pentobarbital (nembutal) given intravenously and symptomatically 40 minutes after a subcutaneous injection of 4 mgm. morphine per kilogram as a basal anesthetic. The anterior portion of the basioccipital and the posterior portion of the basisphenoid bones in the midline were scraped to obtain a clear field and a motor-driven dental burr was used to trephine a hole of ½ to 1 cm. diameter through the skull at this point. An incision of the dura through this opening exposed the basilar artery lying against the pons. The artery was clamped firmly with two pial clips placed side by side at the level of the fifth pair of cranial nerves so that the blood supply of the brain anterior to the clips would come only through the internal carotid arteries. The hole in the skull was filled with bone wax and the incisions sutured. The dog was then given 1 gram of sulfanilamide per kilogram suspended in milk and molasses and placed in the recovery pen. Two to 7 days were allowed for recovery from any traumatic effects of the operation. Some of the dogs showed no nervous manifestations of the operation on the following day while others showed exophthalmos and ataxic movements for three or four days. In the second stage the animal was again placed on a 33 per cent. cyclopropane mixture and injected with the control dose of adrenalin to show that clamping the basilar artery produced no lesions of the brain stem which might affect the length of the resulting ventricular tachycardia. The carotid arteries were next exposed and clamped and 30 to 60 minutes allowed for the dog to become decerebrated by the induced anaemia.

This method produces a satisfactory physiological decerebration in the dog. The cerebrum and midbrain do not always die but simply become depressed below the functional state. This was shown by the fact that several animals, which showed all the characteristic signs of decerebration with the carotids and basilar clamped, apparently recovered within three to ten hours after the carotids were released. If the carotids were again clamped and India ink injected peripherally, a small but definite trace could be seen in the circle of Willis. In order to be certain of decerebration in experiments which were to last longer than two hours the carotids were clamped throughout. By this method

cerebral and midbrain activity can be removed without trauma, hemorrhage, or even the rapid production of necrotic products by dead brain tissue. Therefore, the condition is as near normal as possible for a decerebrate preparation.

Three dogs were decerebrated by tying the innominate and left subclavian arteries at their origin, thereby depriving the entire head of blood. These dogs were considered decerebrate after 15 to 30 minutes of anaemia.

The third method of decerebration was used on only one dog. This was the "bloodless" method of Sollmann in which the brain stem is clamped in the region of the superior colliculi (9).

TABLE I

ADRENALIN INJECTIONS IN DEEP CYCLOPROPANE ANESTHESIA BEFORE AND AFTER DECEREBRATION

Dog No.	Before Decerebration			After Decerebration				
	Adrenalin mg./kg.	Heart rate before Inj.	Effect of adrenalin	Heart rate before Inj.	Carotids clamped	Effect of adrenalin	Protection	Notes
1	0.010	188	VT 72 sec.	155	−	SA 160 1 V Exs	Complete	
2	0.003	160	VT 50 "	95	+	SA 95	"	Repeated with full protection next day
3	0.005	200	VT 60 "	100	−	SA+AV 1 V Exs	"	Decerebrated by Sollmann method
4	0.004	155	VT 46 "	94	+	8 sec. VT	Incomplete	Anastomosis around the basilar artery clips
5	0.008	94	VT 45 "	160	+	SA	Complete	Vagotomy
6	0.008	165	VT 143 "	165	+	SA	"	Vagotomy
7	0.012	150	VT 40 "	135	−	SA 230	"	
8	0.006	250	VT 51 "	60	−	SA+AV	"	SA 115 after 5 minutes
9	0.010	160	VT 38 "	145	−	SA 145	"	
10	0.010	150	VT 33 "	75	+	AV 60 4 V Exs	"	
11	0.006	130	VT 42 "	150	−	SA+AV 188	"	
12	0.004	90	VT 44 "	AV 120	+	AV	"	0.006 mg. Adr./kg under cyclo produced ventricular flutter
13	0.012	125	VT 33 "	136	−	AV 170	"	
				140	+	AV 190	"	
14	0.010	115	VT 50 "	AV 120	+	AV 150 to SA 214	"	Vagotomy
15	0.006	136	VT 50 "	AV 38	−	SA 10	"	Heart rate was 40/min. during preceding 24 hrs.

VT = ventricular tachycardia. AV = auriculo-ventricular rhythm.
SA = sino-auricular rhythm. V Exs = ventricr extrasystole.

After decerebration and with the dogs still in deep anesthesia the control dose of adrenalin was again injected while continuous electrocardiograms were taken. In 8 of the dogs the carotid arteries were released temporarily at the time of the injection in order to allow the

carotid sinuses to function. Direct blood pressure tracings were made in 6 of the dogs.

Table I summarizes the results of adrenalin injections during cyclopropane anesthesia before and after decerebration. The adrenalin dose necessary to bring on ventricular tachycardia before decerebration ranged from 0.003 to 0.012 mgm. per kilogram according to the individual variation of the dogs. This injection of adrenalin produced ventricular tachycardias ranging from 33 to 143 seconds before decerebration. The injection of identical doses after decerebration produced a ventricular tachycardia in just one animal, and this was for a period of only 8 seconds. The incomplete protection in this dog was probably due to only a partial suppression of the center resulting from an anastamosis later found around the basilar artery. The duration of ventricular tachycardia for the 15 dogs before decerebration was 795 seconds and after decerebration 8 seconds.

These results show that decerebration superior to the pons protects an animal under cyclopropane from the ventricular tachycardia regularly seen on the injection of adrenalin in doses of .003 to .012 mgm. per kilo. That this was really protection was further demonstrated by the fact that in 4 animals that showed recovery from the decerebration, tachycardia was again produced by adrenalin injections. The integrity of some nervous center above the pons is thus shown to be necessary to secure the adrenalin response.

TABLE II

INCREASED DOSES OF ADRENALIN UNDER DEEP CYCLOPROPANE ANESTHESIA

Dog No.	Duration of Ventricular Tachycardia							Remarks
	Before Decerebration	After Decerebration						
	Control Dose	Same Dose	2 & 3x's Dose	5x's Dose	10x's Dose	20 & 30x's Dose	Recovery	
2	50″	0″	V Exs 135″		95″	210″	+	
3	60″	0″	0″			50″	+	
5	45″	0″		0″			+	Vagotomy
6	143″	0″		65″			+	Vagotomy
8	51″	0″	0″				+	
9	38″	0″	0″	0″	5″		+	
10	33″	0″	0″				+	
11	42″	0″	0″	90″			+	
12	44″	0″	24″				+	
13	33″	0″	0″	45″			+	
14	50″	0″		V Exs	75″		+	Vagotomy
15	50″	0″		0″			+	

Higher doses of adrenalin were given to 12 of the decerebrate dogs. Table II shows the results. Complete protection from ventricular tachycardia with doses 2 and 3 times as high as the control dose oc-

curred in 6 out of 8 experiments, and 3 animals showed complete protection from doses 5 times greater than the control dose.

However, ventricular tachycardia can be produced in decerebrate dogs if the concentration of adrenalin is high enough. For example, dogs 2, 9, and 14, which had been protected against tachycardia after 2 and 3 times the control dose of adrenalin, responded when the dose was increased 10 times. All of the dogs recovered from the tachycardias due to the increased doses, even though some received 20 to 30 times the amounts given before decerebration. Since ventricular fibrillation did not occur in this series, even with the large doses of adrenalin, it may safely be assumed that there was also protection from this irregularity.

It is recognized that after long periods of anesthesia there may be a general depression of the entire organism. In such cases as well as in animals in poor condition, cyclopropane may not be effective in sensitizing the heart. All protections reported in this paper were demonstrated within a period of less than two and one-half hours after induction. Furthermore, all blood pressure records taken during protection by any of the methods reported show rises, which is evidence that the circulatory mechanisms were in good condition.

THE PATHWAY TO THE HEART

The protection from the injection of adrenalin under cyclopropane after decerebration would seem to indicate that one or both of the agents affected the heart through nervous influences arising in a midbrain region, probably hypothalamic. Evidence for such a view would be to find the necessary pathway from the higher brain centers to the heart. Seven experiments were performed for this purpose.

In each of 2 dogs a hole was trephined through the occiptal bone in the same place as that used in the anemia decerebrations, and a lesion was made in the pons at the level of the fifth nerve. The concentrations of adrenalin with deep cyclopropane anesthesia which produced 42 and 54 seconds of ventricular tachycardia respectively before the lesions failed to produce any ventricular tachycardia after the lesions were made.

Two dogs had the stellate and upper 5 thoracic white chain ganglia removed on both sides. While the control dose of adrenalin immediately before sympathectomy had produced a ventricular tachycardia of 60 and 107 seconds respectively, identical doses after the removal of the chains gave no irregularities. Furthermore, an injection of 2 times the control dose gave only an increased heart rate.

Three dogs were given ergotamine tartrate in doses of $\frac{1}{6}$, $\frac{1}{7}$, and $\frac{1}{8}$ mgm. per kilogram respectively. These concentrations did not prevent blood pressure rises when adrenalin was injected under deep cyclopropane, but there was complete cardiac protection. Figure 1 shows the results of 3 injections of adrenalin into one of these dogs. The blood

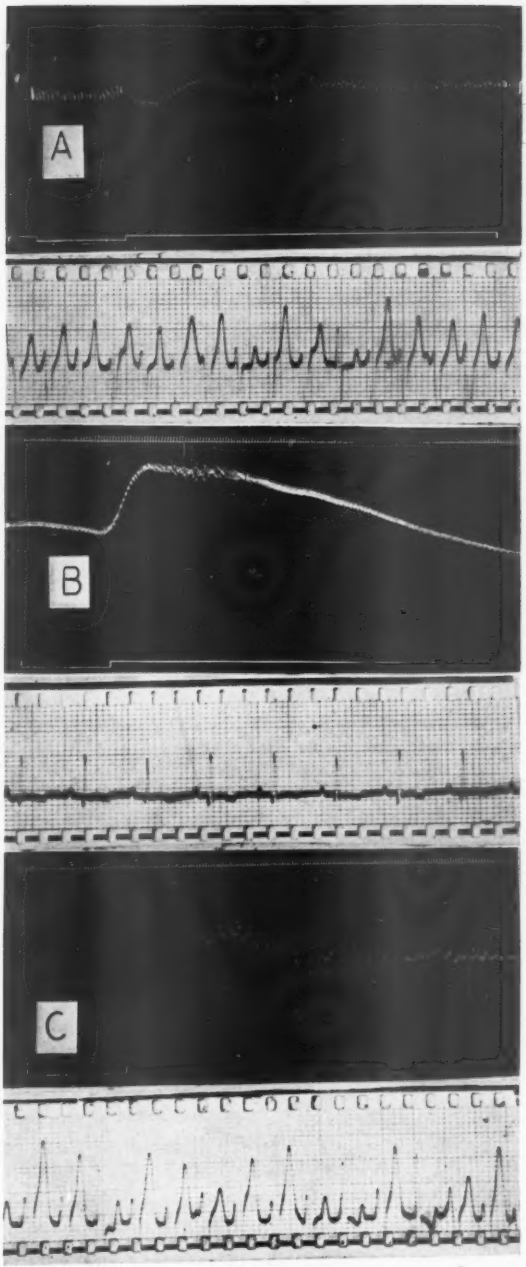

FIG. 1. Blood pressure tracings and electrocardiograms of adrenalin injections under deep cyclopropane anesthesia.

A. Adrenalin control. *B*. Same dose of adrenalin 8 minutes after 1/6 mgm. ergotamine per kilogram. *C*. Adrenalin control 24 hours later.

pressure and electrocardiographic records in *A* were made during an adrenalin injection under deep cyclopropane. The injection resulted in the usual ventricular tachycardia which in this case lasted 60 seconds and prevented any great rise in blood pressure. In record *B* may be seen the results of the same injection under cyclopropane 8 minutes after the intravenous injection of ⅙ mgm. per kilogram of ergotamine. The blood pressure rose from 150 to 220 mm. Hg. The electrocardiogram showed no irregularities. Record *C* is of the injection of the control dose of adrenalin under cyclopropane on the following day with the reappearance of ventricular tachycardia of 70 seconds' duration. Similar records were obtained with the other 2 dogs.

Complete protection from ventricular tachycardia was obtained by lesions of the brain stem, by bilateral thoracic sympathectomy, or by blocking the sympathetics to the heart with ergotamine tartrate. Since all of these experiments conform so completely to the sympathetic pathway worked out by Beattie, Brow, and Long (4) for chloroform stimulation of the heart of the cat, we believe a similar pathway is involved in the cyclopropane sensitization of the heart to adrenalin.

SITES OF ACTION OF ADRENALIN

The site of action of adrenalin in producing ventricular tachycardia was next studied. In 6 dogs prepared for decerebration by clamping the basilar artery, the control dose of adrenalin was injected into the femoral vein immediately after clamping the common carotid arteries and depriving the brain of blood carrying adrenalin. It was assumed that the center necessary for tachycardia under cyclopropane would survive for a few minutes and continue its influence on the heart. In these experiments ventricular tachycardia was produced for periods comparable to those of the controls. Fifteen to 30 minutes later adrenalin was ineffective due to the decerebration which had now occurred.

In 2 dogs the innominate and left subclavian arteries and the superior vena cava were clamped in order to be certain that no blood reached or left the head. Adrenalin was immediately injected above the clamps into the peripheral end of one carotid. It was immediately forced through the head by an injection of saline. In one case the jugular was bled to the exterior in order to insure circulation. There was no ventricular tachycardia in either experiment. Circulation to the head was reestablished. The control dosage of adrenalin was then injected peripherally, and the resultant ventricular tachycardia lasted for periods comparable to those of the controls. This agrees with most of the literature which states that the cardiac action of adrenalin is not by way of medullary centers but directly on the myoneural junctions of the heart.

TABLE III

RELATIONSHIP OF HEIGHT AND ANGLE OF BLOOD PRESSURE RISE TO VENTRICULAR TACHYCARDIA INDUCED BY ADRENALIN INJECTION IN CYCLOPROPANE ANESTHESIA

Dog No.	With Ventricular Tachycardia			Without Ventricular Tachycardia			
	Height		Angle of Initial Rise	Height		Angle of Initial Rise	Protection by
	Before Adrenalin Injection	Maximum Rise To		Before Adrenalin Injection	Maximum Rise To		
	mm. Hg	mm. Hg		mm. Hg	mm. Hg		
2	136	200	53°	120	170	41°	Decerebration
				104	200*	65°	"
9	74	190	67°	70	226*	80°	"
11	154	226	32°	130	150	32°	"
				150	196†	55°	"
12	170	230	40°	174	210	48°	"
13	170	220	58°	152	176	54°	"
14	140	200	60°	130	170	50°	"
				114	210*	63°	"
16	156	170	33°	150	220	67°	Ergotamine
17	138	226	58°	50	130	63°	"
18	136	206	47°	54	110	44°	"
19	110	190	55°	56	164	58°	Sympathectomy

* Five times the control dose of adrenalin.
† Three times the control dose of adrenalin.

ROLE OF BLOOD PRESSURE IN PRODUCING VENTRICULAR TACHYCARDIA

In view of the protection following sympathectomy and of the accepted explanation of the action of ergotamine as blocking the postganglionic sympathetic nerve endings, it seems that this drug prevents the ventricular tachycardia by blocking the sympathetic nerve endings in the heart. That this ventricular tachycardia resulting from the injection of adrenalin during cyclopropane anesthesia is *not* due to the height or abruptness of the rise in blood pressure, as Shen et al. (10, 11) have postulated for adrenalin-chloroform syncope, is shown in Table III. Adrenalin injection into 5 of the 10 dogs with protection produced higher and more abrupt blood pressure rises than before protection. In 8 of the 10 animals the angle of rise is greater than on the control. Furthermore, in a study (7) of 11 different sympathomimetic amines given in cyclopropane anesthesia it has been shown that the production of tachycardia was related to the constitution of the drugs and not to their blood pressure raising power.

CONCLUSIONS

At least one action of cyclopropane is to render the dog's heart more irritable to adrenalin by direct stimulation of a brain center above the pons which sends impulses to the heart by way of the sympathetic nerves. The direct action of adrenalin on the heart thus sensitized produces ventricular tachycardia.

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The Southern Association of Anesthetists will hold a joint meeting with the Section on Anesthesia of the Southern Medical Association which meets in Louisville, November twelfth to fifteenth, 1940. Secretary-Treasurer of the Southern Association of Anesthetists, Dougal M. Dollar, M.D., 706 Heyburn Building, Louisville, Kentucky.

LABORATORY STUDIES ON THE PROPHYLAXIS AND TREATMENT OF VENTRICULAR FIBRILLATION INDUCED BY EPINEPHRINE DURING CYCLOPROPANE ANESTHESIA *

CHARLES L. BURSTEIN, BRUNO A. MARANGONI, ARTHUR C. DEGRAFF AND E. A. ROVENSTINE

CYCLOPROPANE and other anesthetic agents (1) so increase cardiac irritability that ventricular fibrillation may be caused by the administration of small amounts of epinephrine to the subject being anesthetized. There is some clinical evidence that the same reaction may follow the excess secretion of epinephrine.

Oliver and Schafer (2) and Levy (3) were first to observe ventricular fibrillation during chloroform anesthesia following injection of small doses of epinephrine. Meek, Hathaway and Orth (1) have shown that the same effect may be produced during cyclopropane anesthesia. This complication is so feared by anesthetists that many clinics prohibit the use of sympathomimetic drugs for the treatment of circulatory depression when it occurs during cyclopropane anesthesia, and do not permit the local application of epinephrine for vasoconstriction.

In view of the experimental data accumulated by Kochman and Daels (4), by Mautz (5), and by Beck and Mautz (6) to establish that procaine applied locally to the heart reduces the irritability of the myocardium as evidenced by augmentation of intensity of stimulation necessary to produce extrasystoles or ventricular fibrillation, it was of interest to study the effect of procaine on ventricular fibrillation induced by epinephrine during cyclopropane anesthesia (10). This idea was further strengthened by the report of Hermann and Jourdan (7) which showed that following administration of procaine solution a larger dose of epinephrine is necessary to produce ventricular fibrillation during chloroform anesthesia, and by the work of Shen and Simon (8) who have shown that procaine, when administered to dogs simultaneously with epinephrine, protects against ventricular fibrillation.

Since the injection of procaine solution into the circulation of man is frequently followed by untoward reactions, the study was extended to include less toxic substances whose molecule was in part of the same chemical configuration; viz., para-amino benzoic acid, sodium para-amino benzoate, and the calcium double salt of benzyl succinic and *p*-amino benzoic acids. The latter drug has the trade name Paramon.†

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† Supplied by the Seydel Chemical Co.

Method.—Dogs were the only experimental animals used.

Ninety-three experiments were performed on thirty-two animals. Preanesthetic medication consisting of morphine sulphate one mgm. per kilogram and scopolamine hydrobromide 0.04 mgm. per kilogram was injected subcutaneously one hour before each experiment. The closed carbon dioxide absorption technic was utilized for cyclopropane anesthesia. An open airway was assured by the use of an endotracheal tube fitted with an inflatable cuff. Depth of anesthesia was maintained at second plane as evidenced by the loss of the lid reflex and maintenance of intercostal activity. Electrocardiograms (lead II) were taken before, during and after drug administration.

The test injection of epinephrine was that used and recommended by Meek and his associates (1); 0.01 mgm. per kilogram in 5 cc. of normal saline, injected into a jugular vein at the rate of 1 cc. per ten seconds. This dose, according to Cannon (9), is no more than twice the amount which may be secreted physiologically from emotional disturbance.

The dose of procaine, when administered intravenously, was 5 mgm. per kilogram in 5 cc. of normal saline injected at the rate of 1 cc. in ten seconds. When injected into the heart, the dose of procaine was 5 to 10 mgm. per kilogram in 5 cc. of normal saline. Intracardiac injections were rapidly completed.

Para-amino benzoic acid and the calcium double salt of benzyl succinic and *p*-amino benzoic acids were administered intravenously 5 to 10 mgm. per kilogram in 20 cc. of normal saline at the rate of 5 cc. in ten seconds.

Sodium para-amino benzoate was administered intravenously 10 to 40 mgm. per kilogram in 5 cc. of normal saline at the rate of 1 cc. in ten seconds.

1. Studies With Procaine

Epinephrine and procaine were administered during cyclopropane anesthesia and electrocardiographic records were made, using:

(*a*) epinephrine alone,
(*b*) procaine and epinephrine simultaneously,
(*c*) procaine preceding epinephrine,
(*d*) epinephrine preceding procaine.

To obviate the possibility of tolerance to epinephrine the order of drug administration was frequently varied.

Results

A. Epinephrine Alone.—The effects of injecting epinephrine alone were studied in one group of experiments. Nine dogs were used. Six of the animals died of ventricular fibrillation. Figure I illustrates such an effect. Three of these animals, in previous experiments, had been

treated with procaine prior to the intravenous injection of the test dose of epinephrine and had recovered. Following an interval of several days these animals were given an identical dose of epinephrine alone and all three developed ventricular fibrillation.

B. Procaine and Epinephrine Given Simultaneously.—Six dogs were employed. Two of these died of ventricular fibrillation when procaine and epinephrine were given simultaneously. The four surviving animals developed electrocardiographic phenomena referable to the A–V

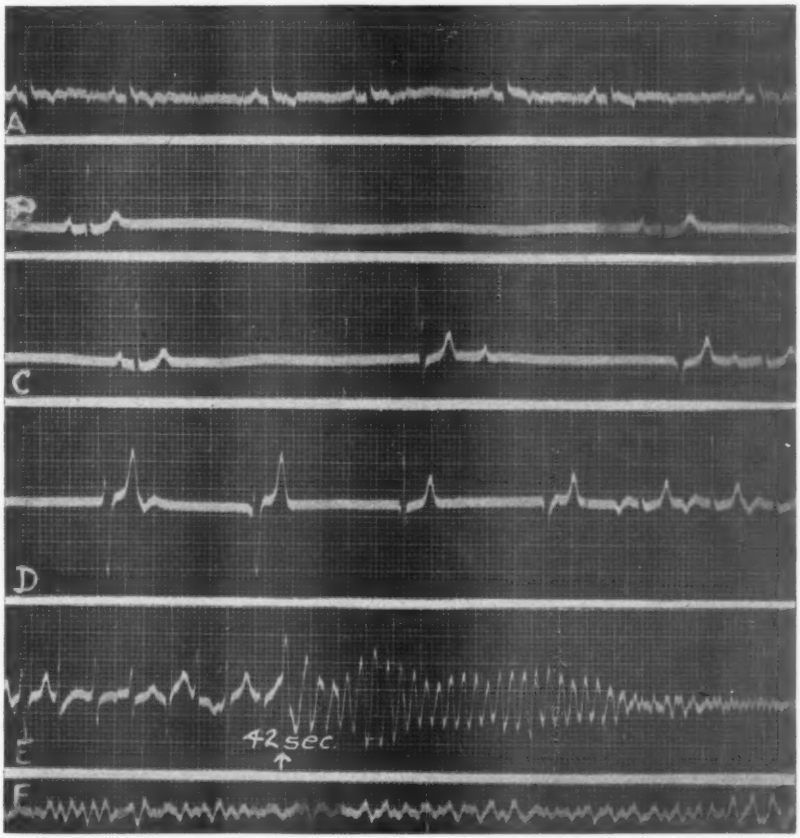

FIG. 1. Dog No. 62, 12.5 kgm. Ventricular fibrillation produced by the intravenous injection of 0.01 mg. per kilo (one test dose) of epinephrine during cyclopropane anesthesia.

A. Control tracing: Sinus arrhythmia.
B. During cyclopropane anesthesia. Note long period of sinus arrest.
C, D, E (continuous tracing). Epinephrine intravenously.
C. Sinus arrest with ventricular escapes.
D. A–V nodal rhythm with ventricular escapes.
E. Ventricular fibrillation—42 seconds after beginning injection of epinephrine.
F. Artificial respiration. No effect on ventricular fibrillation.

node and the ventricles which rapidly shifted back to the sinus node. All revealed increased cardiac rates, which suggest an initial rapid and predominant epinephrine effect with gradual and slower ascendency of the procaine effect and reestablishment of the pacemaking sinus node.

C. Procaine before Epinephrine.—Eight dogs were used; all except one survived. This animal died of respiratory paralysis which preceded cardiac arrest when an amount equal to eight test doses of epinephrine was injected intravenously. This same dog had been studied twice before this fatal termination by injecting procaine 15 minutes before epinephrine, employing one test dose of epinephrine the first time and three test doses the second time, when the only electrocardiographic abnormality consisted of short runs of ventricular tachycardia.

An extremely peculiar and interesting phenomenon was observed in this group; namely absence of an increase in pulse rate, and, in many instances, a diminished rate when epinephrine was administered after a preceding injection of procaine. This observation was noted with regularity. When procaine did not precede the injection of epinephrine, the characteristic effects of the latter drug occurred. This phenomenon is illustrated in the following protocol and accompanying electrocardiographic tracings (Fig. 2):

Dog. No. 33, weight 12 kilos. The control tracing taken before anesthesia (Fig. 2*a*) showed a sinus arrhythmia with a rate of 90 beats per minute. The P–R interval was 0.12 second and the QRS 0.06 second. During cyclopropane anesthesia (Fig. 2*b*) a sinus arrhythmia with periods of sinus arrest and ventricular escapes occurred. Following procaine injection (*c*) the rate increased from 70 to 90 beats per minute. As epinephrine was being injected (*d*) the rate slowed to 60 beats per minute, 14.8 seconds after the beginning of administration of epinephrine and was characterized by a series of sinus arrests with ventricular escapes. The recovery tracing (*e*), with the dog conscious after anesthesia was discontinued, showed the basic rhythm of sinus arrhythmia.

D. Epinephrine before Procaine.—The experiments were completed on seven dogs. The same experiment was repeated in two of the animals. All the animals survived. In five of the animals, after ventricular tachycardia was established following the intravenous injection of a test dose of epinephrine, the injection of a test dose of procaine caused a change to auricular tachycardia which then passed into sinus tachycardia and finally returned to normal. Two of the animals developed ventricular fibrillation when 1.5 and 2 test doses of epinephrine were administered intravenously but both recovered following the intracardiac injection of procaine.

In Fig. 3 is shown the effect of injecting procaine when ventricular tachycardia was established by epinephrine. The control tracing before anesthesia (Fig. 3*a*) showed a sinus arrhythmia with a rate of 80 beats per minute. Ten minutes after the control tracing and during

cyclopropane anesthesia (*b*) the electrocardiogram revealed a sinus tachycardia at a rate of 110 beats per minute. Five minutes later two test doses of epinephrine were injected intravenously in 47.4 seconds. Ventricular tachycardia (*c*) occurred 14.6 seconds after beginning the administration of epinephrine and persisted (*d*) until 8.6 seconds after procaine was injected into the heart when the rhythm changed from ventricular tachycardia to auricular tachycardia. The rhythm finally

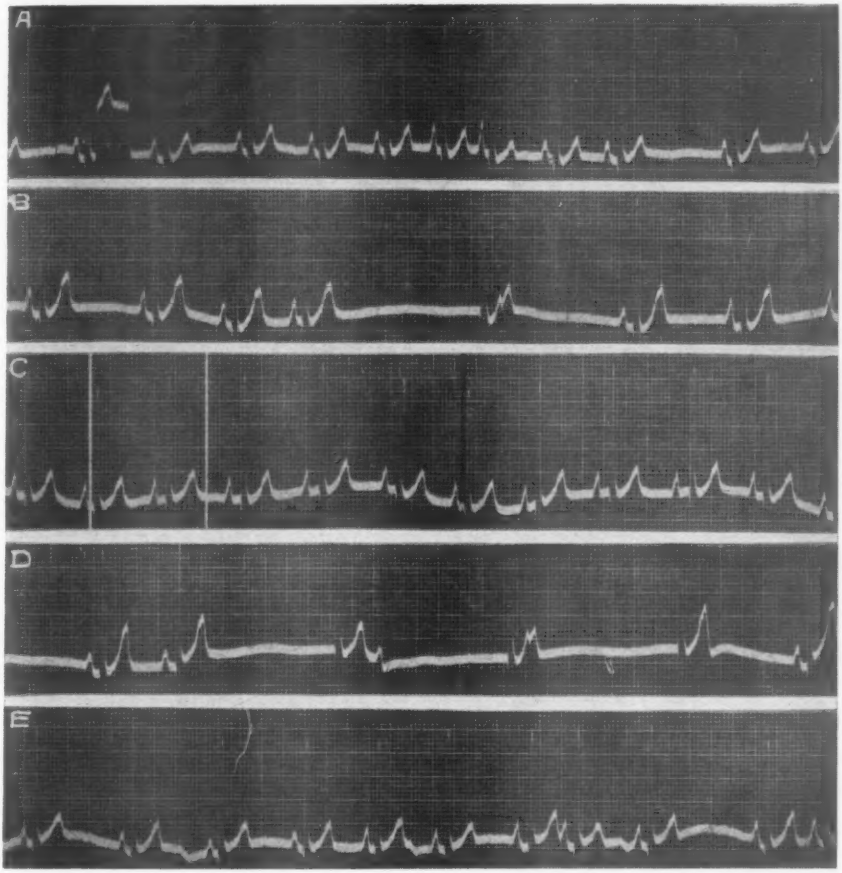

FIG. 2. Dog No. 33, 12 kgm. Administration of procaine before injection of epinephrine.

A. Control: Sinus arrhythmia.

B. Cyclopropane anesthesia—Sinus arrhythmia with periods of sinus arrest and ventricular escapes.

C. End of injection of procaine. Sinus arrhythmia. Sinus arrest and ventricular escapes disappear.

D. During injection of epinephrine. Note slowing in rate from 90 to 60 followed by sinus arrest with ventricular escapes.

E. Recovery. Sinus arrhythmia with auricular premature systoles.

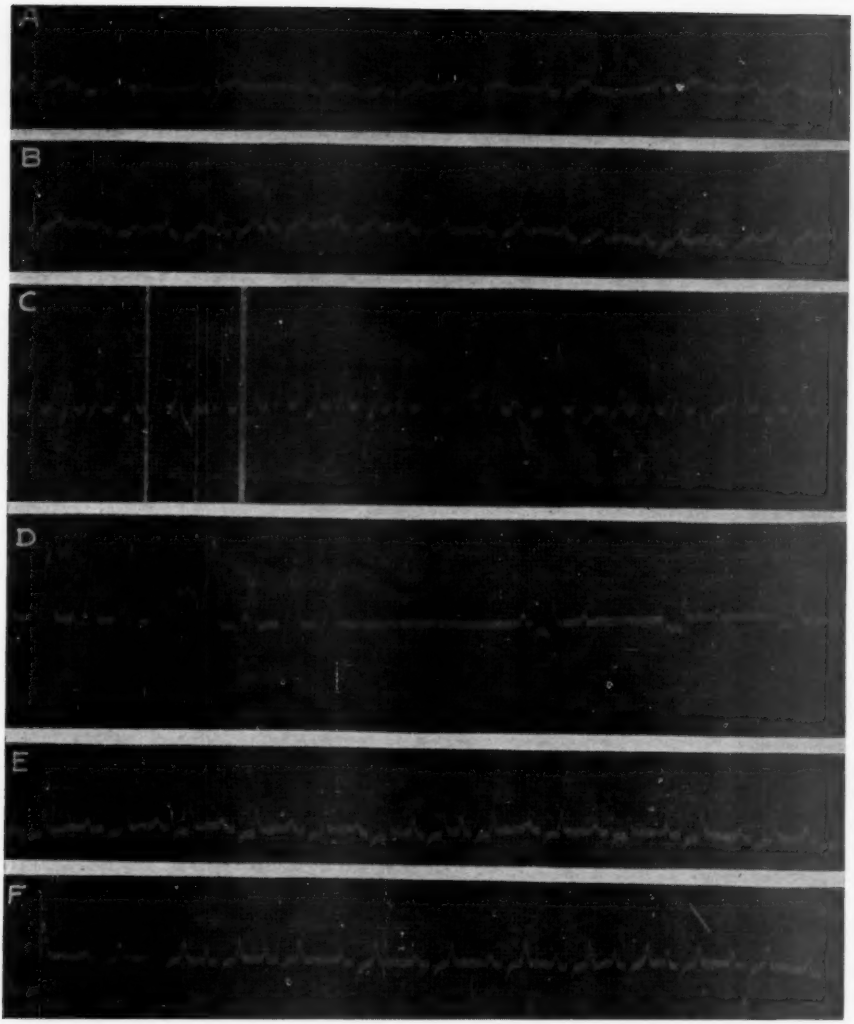

FIG. 3. Dog No. 608, 13.5 kgm. Effect of administration of procaine following development of ventricular tachycardia by epinephrine during cyclopropane anesthesia.

A. Control: Sinus arrhythmia.

B. Cyclopropane anesthesia—Sinus tachycardia and arrhythmia.

C. End of injection of epinephrine. Ventricular tachycardia.

D. Immediately after injection of procaine. Note sudden change from ventricular tachycardia to auricular tachycardia preceded by two blocked auricular premature systoles.

E. Five minutes later. Sinus tachycardia and arrhythmia.

F. Recovery: Sinus tachycardia and arrhythmia.

became a sinus tachycardia (*e*) and when cyclopropane was discontinued (*f*) the recovery tracing showed the normal tracing of sinus arrthythmia.

In Figs. 4 and 5 are presented the results of experiments in which the intracardiac injection of procaine solution during ventricular fibrillation was followed by a return to a normal rhythm.

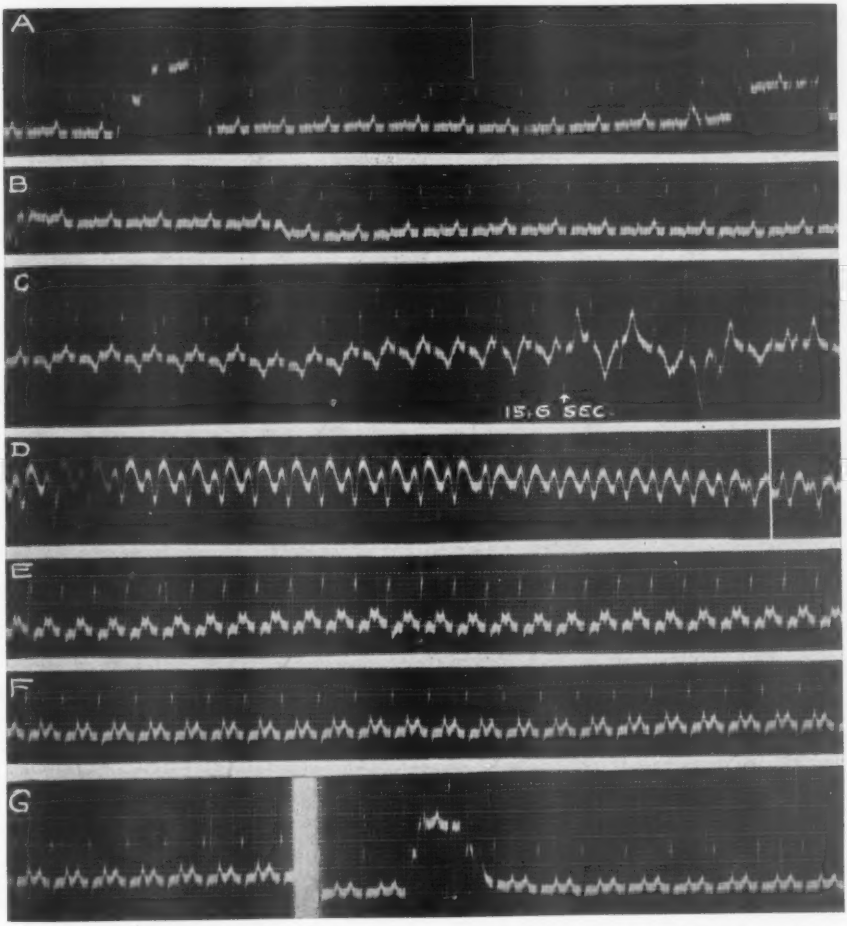

FIG. 4. Dog No. 34, 14 kgm. Effect of intracardiac injection of procaine on ventricular fibrillation produced by epinephrine.

A. Control: Sinus tachycardia.
B. Cyclopropane anesthesia. Sinus tachycardia.
C. 15.6 seconds after beginning injection of epinephrine. Ventricular tachycardia.
D. End of injection of epinephrine. Ventricular fibrillation.
E. After intracardiac injection of procaine. Auricular tachycardia.
F. Recovery: Sinus tachycardia.

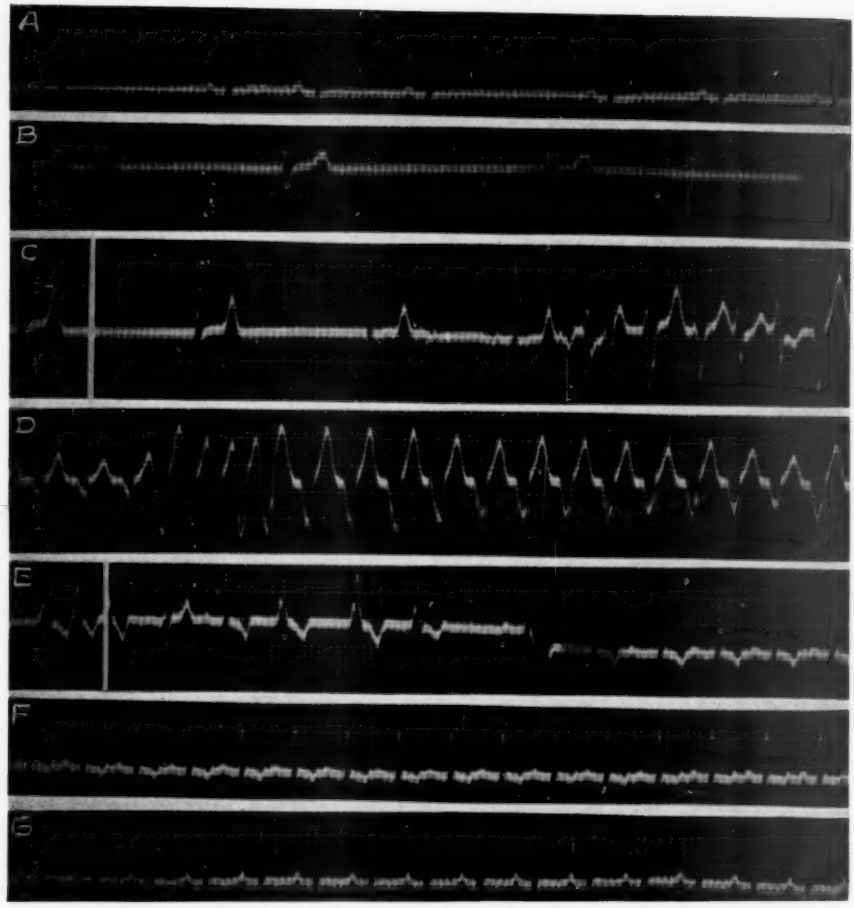

FIG. 5. Dog. No. 41, 7.5 kgm. Another illustration of the effect of intracardiac procaine on ventricular fibrillation.

A. Control: Sinus arrhythmia.

B. Cyclopropane anesthesia. Auricular paralysis with ventricular escapes.

C. End of injection of epinephrine. Sudden onset of ventricular tachycardia lasting 20.4 seconds and then change to ventricular fibrillation.

D. Ventricular fibrillation.

E. End of injection of procaine into heart. The rhythm changes from ventricular fibrillation to sinus tachycardia 4.4 seconds after the injection of procaine into the heart.

F. Sinus tachycardia.

G. Recovery: Sinus tachycardia.

In Fig. 4 it may be seen that following the injection of epinephrine there resulted a ventricular tachycardia (Fig. 4*c*) which was succeeded by ventricular fibrillation (*d*) and that the intracardiac injection of 100 mgm. of procaine hydrochloride in five cc. normal saline (vertical line at end of Fig. *d*) caused a change to auricular tachycardia (*e*). Recovery was then characterized by the basic rhythm of sinus tachycardia (*f*).

In Fig. 5 is shown a similar experiment in which the injection of two test doses of epinephrine during cyclopropane anesthesia caused the development of ventricular tachycardia, at *C*, followed by ventricular fibrillation, at *D*, 68.4 seconds after beginning the injection of epinephrine. Procaine was then injected into the heart and 4.4 seconds later, at *E*, the rhythm rapidly changed to regular sinus tachycardia which persisted and was maintained at recovery when the animal regained consciousness.

2. EFFECTS OF PARA-AMINO BENZOIC ACID

Para-amino benzoic acid, from which the ester procaine is formed, was studied in 13 experiments on five dogs. This drug is poorly soluble and required a larger volume of solvent; 20 cc. of warm saline instead of 5 cc.

Administration of this drug during cyclopropane anesthesia prior to the injection of epinephrine showed a protecting action against the production of cardiac irregularities. When ventricular tachycardia occurred following the injection of epinephrine the administration of para-amino benzoic acid usually caused a return to sinus rhythm, but it was found valueless when ventricular fibrillation had developed. These points are illustrated in Figs. 6 and 7 and in the following protocols:

Protocol I—Dog. No. 31; Weight 11 kgm.

2:05 Control; lead 2.

VR — 65 P–R interval — 0.13
AR — 65 Q.R.S. — 0.05

Impression: Sinus arrhythmia with auricular premature systoles.

2:18 During second plane cyclopropane anesthesia.

VR — 90 P–R interval — 0.11
AR — 90 Q.R.S. — 0.05

Impression: Normal sinus rhythm with auricular premature systoles.

2:21 Following injection of 100 mgm. of para-amino benzoic acid.

VR — 125 P–R interval — 0.13
AR — 125 Q.R.S. — 0.06

Duration of injection of para-amino benzoic acid — 54.8 seconds.
Impression: Sinus tachycardia.

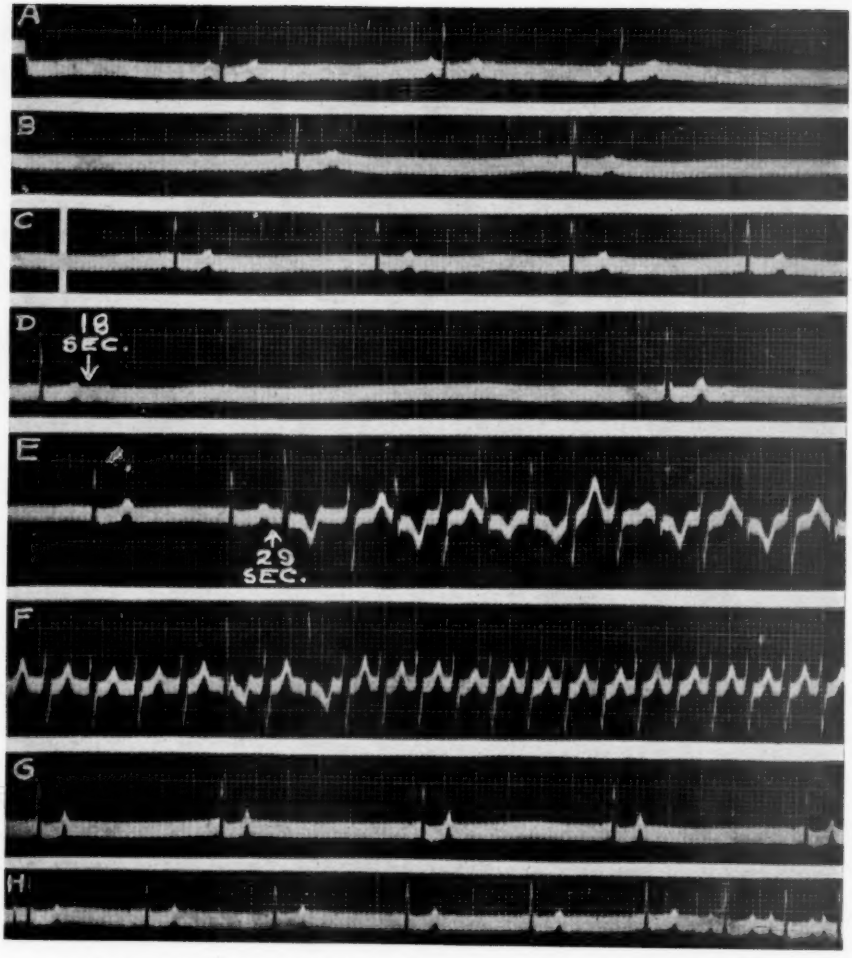

FIG. 6. Dog No. 32, 8 kgm. Administration of para-amino benzoic acid before epinephrine.

A. Control: Sinus bradycardia and arrhythmia.
B. Cyclopropane anesthesia. Sinus bradycardia and arrhythmia.
C. End of injection of para-amino benzoic acid. Auricular paralysis.
D. 18 seconds after beginning injection of epinephrine. Long period of sinus arrest followed by a ventricular escape.
E. 29 seconds after beginning injection of epinephrine. Ventricular tachycardia.
F. 46.6 seconds after beginning injection of epinephrine. Auricular tachycardia.
G. 5 minutes after injection of epinephrine. A–V nodal rhythm.
H. Recovery: Sinus arrhythmia with shifting pacemaker.

2:33 During and following injection of 0.11 mgm. epinephrine.
VR — 90 P–R interval — 0.13
AR — 90 Q.R.S. — 0.05
Duration of injection of epinephrine — 51.8 seconds.
Impression: Sinus arrhythmia with auricular premature systoles. There are no abnormalities or other changes in this tracing.

2:38 Recovery.
VR — 90 P–R interval — 0.13
AR — 90 Q.R.S. — 0.06
Impression: Sinus arrhythmia with auricular premature systoles.

From the above protocol it is seen that the administration of para-amino benzoic acid twelve minutes before the injection of epinephrine,

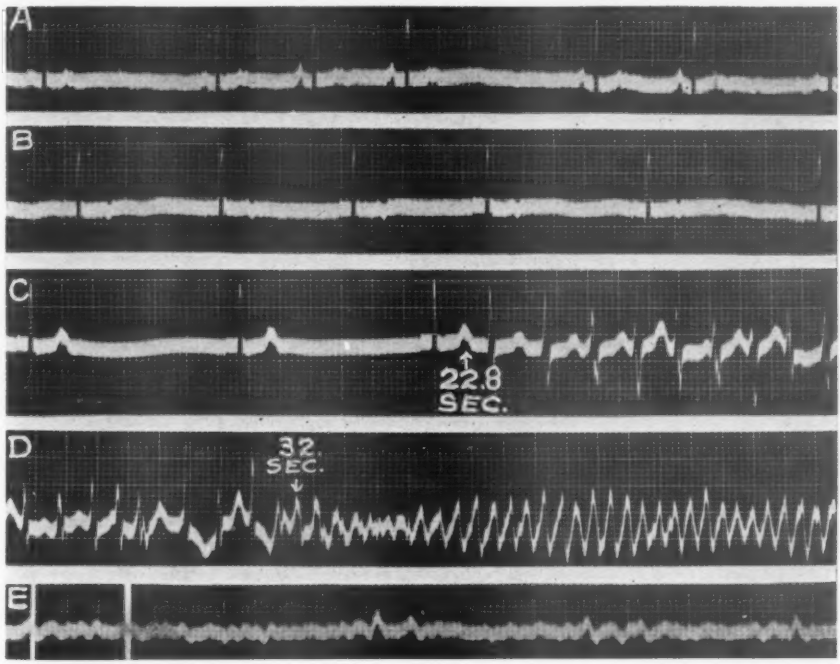

FIG. 7. Dog No. 32, 8 kgm. Ventricular fibrillation when para-amino benzoic acid was not administered before the injection of the same dose of epinephrine as in Fig. 6 on the same animal.

A. Control: Sinus arrhythmia.
B. Cyclopropane anesthesia. Sinus arrhythmia.
C. 22.8 seconds after beginning injection of epinephrine. First interpolated ventricular premature systole, followed immediately by ventricular tachycardia.
D. 32 seconds after beginning injection of epinephrine. Ventricular fibrillation.
E. Intracardiac injection of para-amino benzoic acid. No effect: Ventricular fibrillation.

during cyclopropane anesthesia, caused no alteration in rhythm when one test dose of epinephrine was injected intravenously. Two weeks later the same animal was re-employed but the order of drug administration was reversed. The striking difference in the sequence of events consisted in the production of ventricular tachycardia when the same dose of epinephrine was injected; this ventricular tachycardia then changed to a regular sinus rhythm when the solution of para-amino benzoic acid was injected:

Protocol 2—Dog No. 31; Weight 11 kgm.

1:31 Control ECG—Lead 2.
VR — 80 P–R interval — 0.12
AR — 80 Q.R.S. — 0.06
Impression: Sinus arrhythmia with auricular premature systoles.

1:46 During Cyclopropane Anesthesia.
VR — 70 P–R interval — 0.12
AR — 70 Q.R.S. — 0.06
Impression: Sinus arrhythmia.

1:49 Epinephrine (0.01 mgm. per kilo)
(*a*) 20.4 seconds after beginning of injection a series of ventricular premature systoles occurred.
(*b*) At 44 seconds, ventricular tachycardia set in lasting 43 seconds.
(*c*) The rate then changed to auricular tachycardia with a rate of 240 beats per minute.

1:53 Para-amino benzoic acid.
VR — 110 P–R interval — 0.11
AR — 110 Q.R.S. — 0.05
Impression: Sinus tachycardia.

1:57 Recovery.
VR — 130 P–R interval — 0.11
AR — 130 Q.R.S. — 0.05
Impression: Sinus tachycardia with arrhythmia.

An even more striking protecting action by para-amino benzoic acid is illustrated in Figs. 6 and 7 which present the electrocardiographic tracings taken on the same dog when two test doses of epinephrine were injected intravenously during cyclopropane anesthesia. In Fig. 6 where para-amino benzoic acid was administered five minutes before epinephrine, it will be observed that during the injection of two test doses of epinephrine ventricular tachycardia set in (Fig. 6*e*) 29 seconds after beginning the injection of epinephrine and lasted 17.6 seconds when the rhythm changed to auricular tachycardia (*F*) and then to an A–V nodal rhythm (*G*) followed by recovery to a sinus arrhythmia (*H*).

Three days later, a similar experiment was repeated on the same animal but para-amino benzoic acid was omitted. The same dose of epinephrine was prepared for administration and ventricular fibrilla-

tion occurred rapidly (Fig. 7*d*) 22.8 seconds after the beginning of injection of epinephrine when only half of the solution was injected. 100 mgm. of para-amino benzoic acid was then injected into the heart but had no effect on the ventricular fibrillation and the dog succumbed.

3. EFFECTS OF THE CALCIUM DOUBLE SALT OF BENZYL SUCCINIC AND *P*-AMINO BENZOIC ACIDS

The calcium double salt of benzyl succinic and *p*-amino benzoic acids was found to be about twice as soluble as para-amino benzoic acid. Its effects were studied in 21 experiments on 9 dogs with results similar to those obtained by para-amino benzoic acid. Some examples of these effects are presented from the studies of various conditions attempted upon one of these animals.

A typical effect of the differences in reaction when this drug was administered before the injection of a test dose of epinephrine during cyclopropane anesthesia as compared to its administration after epinephrine is presented in the following two protocols of experiments performed on the same animal:

Protocol 3—Dog No. 34, 14 kgm.

1:35 Control; lead 2.
VR — 70 P–R interval — 0.15
AR — 70 Q.R.S. — 0.07
Impression: Sinus arrhythmia.

1:50 Cyclopropane anesthesia.
VR — 60 P–R interval — 0.17
AR — 60 Q.R.S. — 0.06
Impression: Sinus arrhythmia.

1:55 The calcium double salt of benzyl succinic and *p*-amino benzoic acids (60 mgm.) intravenously.
Duration of injection: 50.4 seconds.
VR — 60 P–R interval — 0.18
AR — 60 Q.R.S. — 0.07
Impression: Sinus arrhythmia.

2:00 Epinephrine (0.01 mgm. per kilo) intravenously.
Duration of injection: 51.6 seconds.
VR — 55 P–R interval — 0.17
AR — 55 Q.R.S. — 0.06

(*a*) 20.6 seconds after beginning injection of epinephrine the first ventricular escape occurred.

(*b*) 23.6 seconds after beginning of the injection a run of ventricular escapes occurred followed by a return to the control rhythm.

2:10 Recovery from anesthesia.
VR — 80 P–R interval — 0.15
AR — 80 Q.R.S. — 0.06
Impression: Sinus arrhythmia.

Protocol 4—Dog No. 34, 14 kgm.

1:35 Control; lead 2.
VR — 70 P–R interval — 0.17
AR — 70 Q.R.S. — 0.06
Impression: Sinus arrhythmia.

1:50 Cyclopropane anesthesia.
VR — 50 P–R interval — 0.16
AR — 50 Q.R.S. — 0.06
Impression: Sinus bradycardia and arrhythmia.

1:55 Epinephrine (0.01 mgm. per kilo) intravenously.
Duration of injection: 51.2 seconds.
VR — 50–130 (near end of injection) P–R interval — 0.16
AR — 50–130 (near end of injection) Q.R.S. — 0.06
Impression: Sinus bradycardia going to sinus tachycardia with a short run of A–V nodal rhythm. This was followed by ventricular tachycardia.

(*a*) 24.8 seconds after beginning of injection, the first ventricular premature systole occurred.

(*b*) 32.2 seconds after beginning of injection a short run of A–V nodal rhythm occurred lasting for six complexes.

(*c*) 40.2 seconds after beginning of injection ventricular tachycardia occurred.

1:58 The calcium double salt of benzyl succinic and *p*-amino benzoic acids (60 mgm.) intravenously.
VR — 80 P–R interval — 0.17
AR — 80 Q.R.S. — 0.05
Impression: Regular sinus rhythm.

2:15 Recovery (Dog awake and active).
VR — 120 P–R interval — 0.15
AR — 120 Q.R.S. — 0.06
Impression: Sinus tachycardia and arrhythmia.

The above two protocols of experiments performed upon the same dog at a weekly interval show that whereas only a few ventricular escapes occurred following the intravenous injection of one test dose of epinephrine when the calcium double salt of benzyl succinic and *p*-amino benzoic acids had been administered five minutes previously, the cardiac irregularities were more severe when it did not precede epinephrine since then, the same dose of epinephrine resulted in A–V nodal rhythm, followed by ventricular premature systoles and finally by ventricular tachycardia.

When the dose of epinephrine was increased to 1.5 test doses the protecting action of the calcium double salt of benzyl succinic and *p*-amino benzoic acids, as shown in Figs. 8, 4, and 9, was even more evident.

In Fig. 8 it is shown that no irregularities occurred when it was administered before the intravenous injection of 1.5 test doses of epinephrine during cyclopropane anesthesia.

When the same dose of epinephrine was injected in the same manner into the same animal eight days later but without the previous administration of the calcium double salt of benzyl succinic and *p*-amino benzoic acids, ventricular fibrillation occurred (Fig. 4*D*). The intracardiac injection of 100 mgm. of procaine in 5 cc. saline then caused a change from ventricular fibrillation to auricular tachycardia (4*E*) and finally full recovery (4*F*).

Two weeks later the same dose of epinephrine was re-injected into the same animal and ventricular fibrillation occurred again (Fig. 9*D*). The calcium double salt of benzyl succinic and *p*-amino benzoic acids, injected into the heart, was then ineffective (Fig. 9*E*).

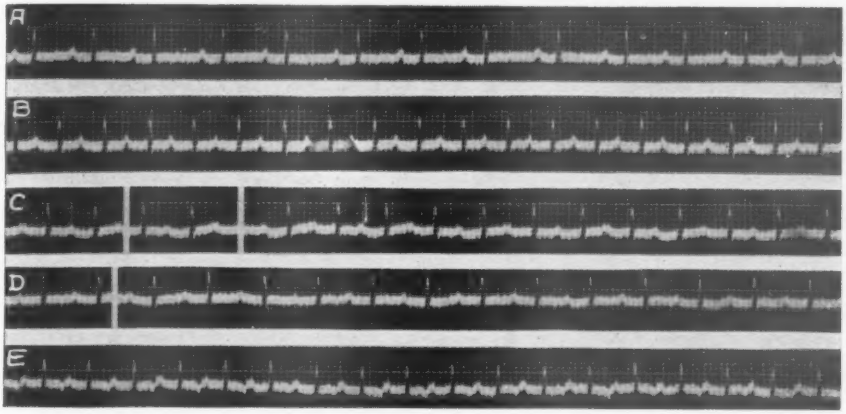

FIG. 8. Dog No. 34, 14 kgm. Administration of the calcium double salt of benzyl succinic and *p*-amino benzoic acids before 1.5 test doses of epinephrine.

A. Control: Sinus tachycardia and arrhythmia.

B. Cyclopropane anesthesia. Sinus tachycardia.

C. End of injection of the calcium double salt of benzyl succinic and *p*-amino benzoic acids. Sinus tachycardia.

D. End of injection of epinephrine. Sinus tachycardia.

E. Recovery: Sinus tachycardia (Rhythm regular).

4. EFFECTS OF SODIUM PARA-AMINO BENZOATE

Sodium *p*-amino benzoate * is readily soluble. Large amounts of the drug could be used conveniently. Doses of 20 mgm. to 40 mgm. per kilo were employed and found to have effects similar to those of para-amino benzoic acid. Sixteen experiments on 7 dogs were completed.

An example of the results obtained is presented in Figs. 10 and 11.

In Fig. 10, following the injection of 1.5 test doses of epinephrine, four minutes after the administration of 40 mgm. per kilo of sodium *p*-amino benzoate, there developed an auricular tachycardia (*D*) followed by ventricular tachycardia (*E*). At *F*, 75.6 seconds after the

* Supplied through the courtesy of E. R. Squibb & Sons, New York.

beginning of injection of epinephrine, there was an attempt to shift back to the sinus node and establish a sinus rhythm which succeeded subsequently as shown in *G*.

In Fig. 11 are shown the results obtained in the same animal three days later by injecting the same dose of epinephrine during cyclopropane anesthesia without previously administering any other drug. In this case, ventricular fibrillation occurred suddenly and rapidly, at *C*, when only ⅔ of the dose of epinephrine was injected.

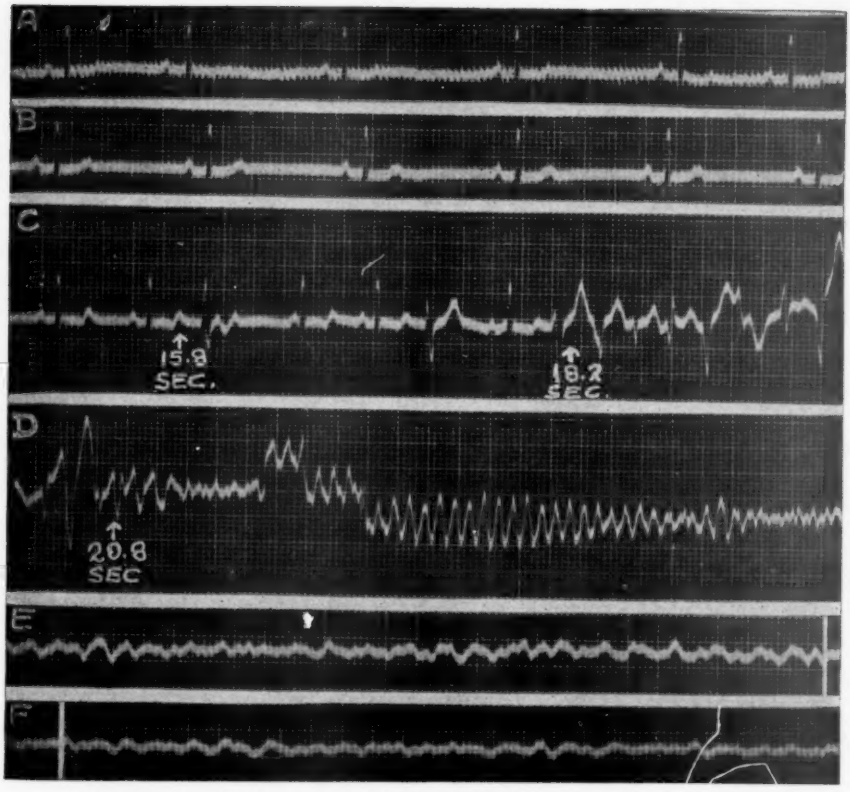

FIG. 9. Dog No. 34, 14 kgm. Ventricular fibrillation induced by 1.5 test doses of epinephrine (same as in Fig. 8) when the calcium double salt of benzyl succinic and *p*-amino benzoic acids was not administered previously.

A. Control: Sinus arrhythmia.

B. Cyclopropane anesthesia. Regular sinus rhythm.

C. 15.8 seconds after beginning injection of epinephrine. First ventricular premature systole.

D. 18.2 seconds after beginning injection of epinephrine. Short run of ventricular tachycardia followed 2.6 seconds later by ventricular fibrillation.

E–F. Intracardiac the calcium double salt of benzyl succinic and *p*-amino benzoic acids. Ventricular fibrillation; no effect.

DISCUSSION AND CONCLUSIONS

The four series of experiments described above support the contention that the incidence of ventricular fibrillation following the administration of epinephrine to dogs during cyclopropane anesthesia is reduced when procaine, or related chemical compounds studied, is administered prior to epinephrine. Under the conditions described it was

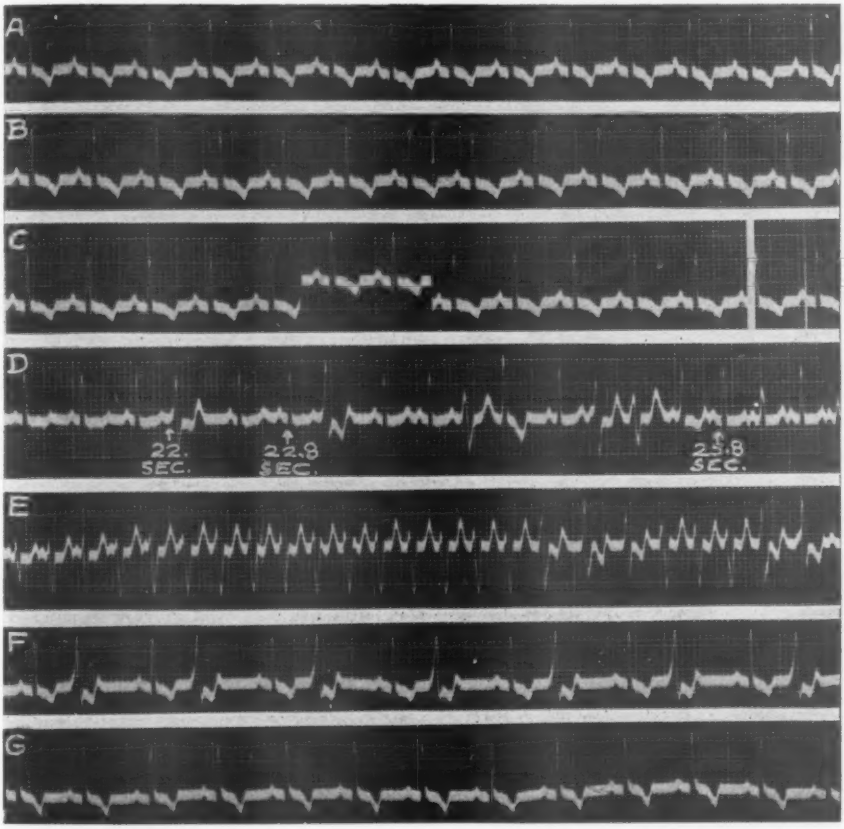

FIG. 10. Dog No. 53, 10 kgm. **Administration of sodium para-amino benzoate before 1.5 test doses of epinephrine.**

A. Control: Sinus tachycardia.

B. Cyclopropane anesthesia. Sinus tachycardia.

C. End of injection of sodium para-amino benzoate. Sinus tachycardia.

D. 22 seconds after beginning injection of epinephrine. First ventricular premature systole.

27.8 seconds after beginning injection of epinephrine. Auricular tachycardia.

E. 47.4 seconds after beginning injection of epinephrine. Ventricular tachycardia.

F. 75.6 seconds after injection of epinephrine. Normal sinus rhythm. Ventricular premature systoles with coupling. Recovery taking place.

G. Recovery: Sinus tachycardia.

found that six dogs out of nine died of ventricular fibrillation when one test dose of epinephrine, consisting of 0.01 mgm. per kilo, was injected intravenously into a jugular vein in 50 seconds during the second plane of cyclopropane anesthesia. When procaine (5 mgm. per kilo), *p*-amino benzoic acid (5 mgm. per kilo), the calcium double salt of benzyl succinic and *p*-amino benzoic acids (5 mgm. per kilo) or sodium *p*-amino benzoate (10 to 40 mgm. per kilo) was administered before the same test dose of epinephrine during cyclopropane anesthesia, only two dogs out

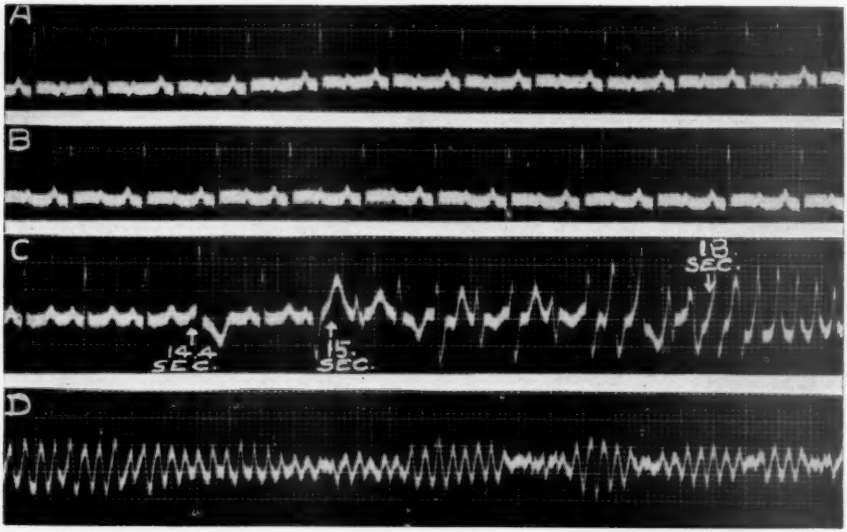

FIG. 11. Dog No. 53, 10 kgm. Ventricular fibrillation produced by 1.5 test doses of epinephrine (same as in Fig. 10) when sodium para-amino benzoate was not administered previously.

A. Control: Sinus tachycardia.

B. Cyclopropane anesthesia—Sinus tachycardia.

C. 14.4 seconds after beginning injection of epinephrine; first ventricular premature systole.

15.0 seconds after beginning injection of epinephrine; ventricular tachycardia.

18.0 seconds after beginning injection of epinephrine; ventricular fibrillation (when only ⅘ of the dose of epinephrine was injected).

D. Ventricular fibrillation.

of 26 developed ventricular fibrillation. Both of these dogs showed such marked emotional agitation prior to being anesthetized as to suggest the possibility of excess epinephrine secretion being an additive factor to the epinephrine administration.

Since the intravenous administration of a toxic drug like procaine, under conditions where epinephrine itself is toxic, would seem to be a hazardous procedure clinically, less toxic chemical substances related to procaine were included in this study. All showed similar beneficial

effects in protecting against ventricular fibrillation induced by epinephrine when they were administered before epinephrine. Sodium *p*-amino benzoate because of its greatest solubility is preferred.

The results also indicate that procaine was the only drug studied which was found efficient in the treatment of ventricular fibrillation induced by epinephrine during cyclopropane anesthesia. In each instance when procaine was injected intravenously at the time ventricular tachycardia occurred following the administration of epinephrine, recovery was effected. Similar treatment after ventricular fibrillation developed was effective in 4 of 6 cases when given by intracardiac injection.

Despite the known toxicity of procaine, its use in the treatment of ventricular fibrillation induced by epinephrine seems logical. It has been shown that epinephrine sensitizes the automatic tissue of the heart (1) but procaine reduces this irritability, and increases the threshold for stimuli necessary to produce fibrillation (6). It must be emphasized that in view of the greater toxicity of procaine in man this treatment should be reserved for cases in which no other alternative is present.

SUMMARY

1. Ventricular fibrillation may be inaugurated in the dog by injecting small doses of epinephrine (0.01 mgm. per kilo) during cyclopropane anesthesia.

2. Procaine, and the related chemical compounds studied: *p*-amino benzoic acid, the calcium double salt of benzyl succinic and *p*-amino benzoic acids, sodium *p*-amino benzoate, when administered before epinephrine, protected from this type of ventricular fibrillation.

3. Procaine administered intravenously, when ventricular tachycardia followed the injection of epinephrine, arrested the progression to ventricular fibrillation and recovery to normal occurred after a shifting of the pacemaker to the auricles and finally to the sinus node.

4. The intracardiac injection of procaine was found to be efficient in the treatment of 66 per cent. of animals having developed ventricular fibrillation following epinephrine injection during cyclopropane anesthesia.

We wish to thank Dr. Charles E. Kossmann for his valuable suggestions and Miss B. Rader for her technical assistance.

477 FIRST AVENUE

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SCIENTIFIC PROGRAM OF REGULAR MEETING OF THE AMERICAN SOCIETY OF ANESTHETISTS

745 FIFTH AVENUE, NEW YORK CITY

October 10, 1940—8 P.M.

1. Nupercaine 1:1500 and Dextrose Solution for Spinal Anesthesia —25 minutes.

   By

   R. J. Whitacre, M.D. and B. B. Sankey, M.D., Huron Road Hospital, East Cleveland, Ohio. Discussion to be opened by Meyer Saklad, Providence, R. I.

2. Influence of Preanesthetic Narcotics on Nausea and Vomiting During Spinal Anesthesia—20 minutes.

   By

   Priscilla Sellman, M.D. (By Invitation), Lahey Clinic, Boston, Massachusetts. Discussion to be opened by R. J. Whitacre, Cleveland, O.

3. The Early Recognition of Shock and Its Treatment—50 minutes.

   By

   Charles R. Drew, M.D. (by invitation), Assistant Professor of Surgery, Howard University, College of Medicine, Washington, D. C. Discussion to be opened by Virginia Apgar, M.D., New York City.

OXYGEN THERAPY AND RESUSCITATION *

ERNEST H. WARNOCK, M.D., *Resident Anesthetist*
AND
RALPH M. TOVELL, M.D., *Attending Anesthetist*
Hartford Hospital, Hartford, Connecticut

IN the time of Harvey, the function of respiration was considered to be that of cooling the blood. Conflicting ideas existed concerning the physiology of respiration but in 1666 Boyle showed conclusively that in the absence of air, life was impossible. The true conception of the physiology of respiration as we recognize it today was suggested by Mayow in 1673. He stated that the air contained a certain "nitro-aerial" spirit which was absorbed by the blood in the lungs, eventually reaching the muscles where it initiated muscular contraction through its union with sulphur. In 1774 this same substance was isolated in pure form by Priestley and was called "dephlogisticated air." During his experiments, Priestley showed that this respirable gas was necessary for the conversion of venous into arterial blood (1). Lavoisier in 1777 also isolated the gas and showed that it combined with carbon to form carbon dioxide and that in this combination, animal heat was produced. The results of these and other findings soon led to the use of oxygen by inhalation as a treatment for a wide variety of conditions in a great number of which its use was unsuccessful. Hence, oxygen soon became discredited as a therapeutic agent.

The status of oxygen as a therapeutic agent remained questionable until the time of the World War when Haldane, Barcroft, Hunt, Dufton, and others used it successfully in the treatment of soldiers suffering from exposure to poisonous gases (2). Since that time oxygen therapy has been scientifically investigated. At present it is gaining recognition as a therapeutic agent for an increasingly large number of conditions.

The delayed recognition of the therapeutic value of oxygen is a result of misconceptions. When it was first used, it was thought to be a panacea. This idea is substantiated by the fact that in 1798 Thomas Beddoes established a pneumatic institution at Clifton where oxygen was administered to patients, regardless of the cause of their illness. Such unscientific use of oxygen led to its failure in many instances. The early clinical signs of oxygen want were frequently not recognized and oxygen was not administered until after irreparable damage had been done. Fear of overdosage and inefficiency of apparatus has in the

* Read before the joint meeting of the American Society of Anesthetists, Inc. and the Pacific Coast Association of Anesthetists, December 14, 1939, Los Angeles, Calif.

past prevented the use of oxygen in sufficient concentration to relieve the patient of anoxemia. There are those who have used oxygen, not as a therapeutic aid to the patient, but as a means of convincing the patient's relatives that everything possible was being done. In recent years clinicians have learned to recognize the symptoms of oxygen want and they have become aware of the often irreparable damage which lack of oxygen may produce (3). As a result, an increasing demand is being made for more efficient equipment and a more thorough understanding of the requirements for oxygen in various diseases. Cohen states, "Oxygen to be efficacious must be used freely, frequently, fearlessly, and almost constantly, nor must its use be postponed until the patient is moribund for it will not revive the dead" (4).

Anoxemia may be subdivided into two classes, namely, chronic and acute. Chronic anoxemia is that form which occurs constantly in varying degrees. It is the type seen in individuals suffering from congenital heart lesions. In this type of anoxemia, oxygen therapy is less beneficial than for the acute type. Although the concentration of oxygen in the blood is below normal, the chronicity of the condition permits the body to adjust itself to a reduced content of oxygen in the blood. After this adjustment has been accomplished, increase of the content of oxygen in the blood will not be needed unless some acute condition is superimposed on the chronic one (5).

Acute anoxemia (6) may be subdivided into three types, namely, anoxic, anemic, and stagnant. Anoxic anoxemia exists when the arterial blood does not contain the normal amount of oxygen because of alteration in the oxygen content of the surrounding atmosphere or because of an impaired exchange of gases in the respiratory system. This type of anoxemia is found in mountain sickness and in pneumonia. Anemic anoxemia exists when there is a deficiency or alteration of the hemoglobin making it impossible for the blood to carry sufficient oxygen from the alveoli to the tissues. This is the condition found in cases of anemia. Stagnant anoxemia results when, owing to local or general circulatory causes, the rate of transfer of gas from the lungs to the tissues may be so slow that the hemoglobin becomes "emptied" of oxygen before the journey's end. This type is encountered in cases of cardiac failure. Peters (7) and Van Slyke add a fourth classification, histotoxic anoxia in which the supply of O_2 may be perfectly normal but the cells are poisoned and unable to utilize it properly. This is true of carbon monoxide poisoning.

Depletion of oxygen in the gastro-intestinal system is indicated by the occurrence of nausea, diarrhea and vomiting. The symptoms of lack of oxygen in its early stages that are referable to the respiratory system are increased rate and depth of respiration. Subsequently they are rapid and shallow. In the circulatory system deficiency of oxygen manifests itself by a constant and progressive increase in

pulse rate. If the deficiency is prolonged, there is a decrease in diastolic blood pressure with concurrent cardiac failure. Oxygen want within the central nervous system is manifested by headache, visual disturbances, irrational states, delirium, hyperpyrexia coma, and finally death.

Krogh (8) found that a lack of oxygen in the system increased the permeability of the capillaries. With this increase in permeability there ensues a loss of blood plasma into the tissues. This in turn leads to a concentration of the corpuscles in the capillaries and a decreased blood volume. The increased concentration of the blood leads to a reduced volume flow which further reduces the amount of oxygen which is delivered to the tissues. With deficient oxygenation there is an accumulation of products (9) which tend to produce atony and dilation of the capillaries. This likewise reduces blood volume flow. This vicious circle is present in a large number of acute infections and has often been misinterpreted as a toxemic reaction. If hyperpyrexia is present, this sequence of events may vary somewhat. Alkalosis (10) develops and the slightly alkaline hemoglobin compound gives up its oxygen less readily than normal hemoglobin. With the resulting decrease in arterial oxygen tension there is also associated another factor that tends to increase the severity of this condition. With each increase in temperature of 1° F. the basal metabolic rate increases 5.5 per cent. and with it the demand for oxygen increases (11). The velocity of the blood flow through the capillaries increases, but after the heart has exceeded its maximal effectiveness, and as blood pressure falls, the accelerated velocity may be replaced by comparative stagnation in the dilated vessels. The inhalation of oxygen is a logical procedure in many conditions where this vicious circle is present. Krogh found that the capillary stasis resulting from deficiency of oxygen became irreversible after approximately fifteen minutes. Hence it is essential that remedial measures to be effective must be instituted early.

Since oxygen is becoming recognized as a valuable therapeutic agent in certain diseases and since the medical profession is realizing that unsatisfactory results have in many instances been due to errors in administration, many are becoming interested in improving the efficiency and technique of oxygen therapy. Various methods have been advocated, each of which has been satisfactory in the hands of a few but none has met with universal approval. Oxygen has been administered by mouth in the form of a souffle, made by bubbling oxygen through water to which foam extract has been added (12). It has also been used intravenously. However, the general method of administration has been by inhalation. One of the first methods of administration was by means of the inverted funnel to which was attached a tube and bubble bottle containing water. This method has been found useless in that it was wasteful of oxygen, unpleasant to

wear, and it increased the concentration of oxygen in the inspired air by about two per cent.

The method (13) whereby an intranasal catheter was employed was devised by Adrian Stokes during the World War I. Its chief advantage was in the fact that several patients could be treated simultaneously from one tank of oxygen. However, since the World War I the catheter method has been widely employed, and it is thought by some to be the method of choice.

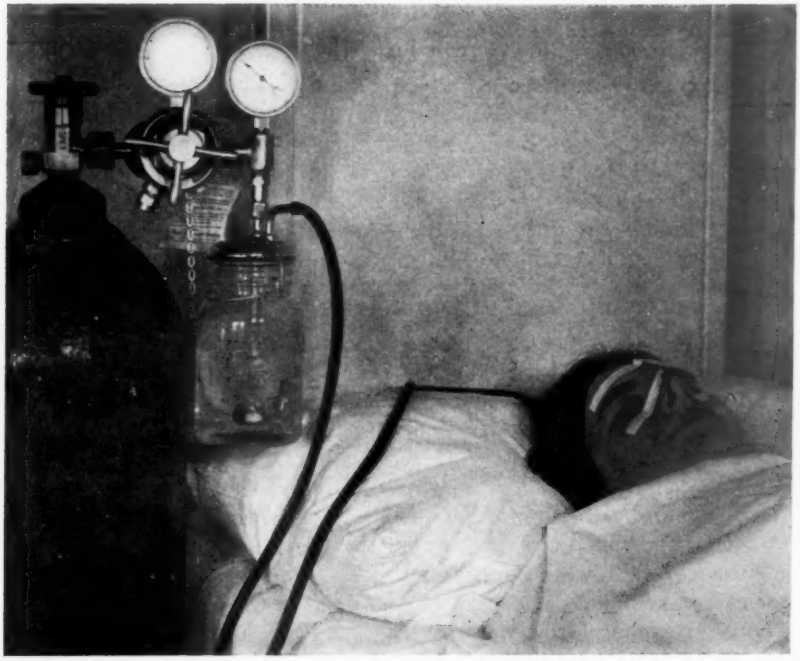

FIG. 1. Oxygen that has been adequately humidified is being administered intranasally.

One of the chief objections to the administration of oxygen by the intranasal method had been the occurrence of drying of the mucous membrane of the nasopharynx as a result of insufficient moisture in the oxygen. This caused the patient discomfort and resulted in infection of the naso- and oro-pharynx. In order to meet this objection, a type of apparatus has been developed, in which conventional types of reducing valves and gauges to indicate tank pressure and oxygen flow are utilized. Attached to this set of valves by means of a metal tube is a closed cylinder, the wall of which is an alloy, which, due to its porous texture, is permeable to gases. This cylinder is immersed in water,

which is contained in an ordinary fruit jar of quart size. The lid of the jar, which fits tightly, contains an outlet through which the oxygen is delivered to the patient. The essential feature of this apparatus (Fig. 1) is that the oxygen in passing through the porous wall of the cylinder becomes finely dispersed, and a larger surface is exposed for the absorption of moisture as the bubbles rise to the surface of the water. Its chief advantage is that oxygen carrying sufficient moisture to insure the comfort of the patient can be administered. When the apparatus is in operation over a twenty-four hour period there is an appreciable lowering of water level in the container, thereby demonstrating the fact that the oxygen in passing through the water does absorb moisture freely.

There are certain precautions which must be taken in order to insure satisfactory performance of this type of outfit. First the tip of the catheter must be accurately placed in the oro-pharynx. Faulty placement will result in marked reduction of the concentration of oxygen in the lung. If the catheter is inserted too far into the pharynx the patient will swallow oxygen which will produce a dilatation of the stomach. It is also necessary that the water level in the container be kept within proper limits. Too low a level reduces the absorption of moisture, while with too high a level, water will flow into the intranasal catheter. The proper level can be indicated on the jar.

It is felt that this apparatus possesses advantages over those of similar type. Its simplicity of construction and ease of installation are worthwhile factors. It does permit adequate humidification of the oxygen. The parts of the apparatus which may be broken are freely available and they are inexpensive.

The same apparatus may be used to deliver oxygen or oxygen and helium mixtures to a B.L.B. mask of either the nasal or oro-nasal types (Fig. 2). These masks are particularly useful for the administration of high concentrations of oxygen for the relief of abdominal distention, or for the relief of severe anoxia associated with pneumonia or cardiac decompensation. For the administration of mixtures of helium and oxygen in the treatment of status asthmaticus two regulators and humidifiers are employed. One is attached to a tank containing helium 80 per cent. and oxygen 20 per cent. and the other is attached to a tank containing only oxygen. The delivery tubes are connected through a Y to a B.L.B. mask of the oro-nasal type. Helium may be given in 80 per cent. concentration or additional oxygen may be added if signs of deficiency of oxygen are present.

An oxygen tent of standard make operated under proper supervision furnishes an excellent and economical means of administering oxygen. In the selection of a tent there are certain fundamental principles which should be recognized. The motor should be mechanically efficient and readily controllable. There should be sufficient space so that the patient will not feel restricted. Means should be provided for

variation of the rate of circulation and height of temperature in the tent. Adequate means for controlling humidity and for controlling the concentration of carbon dioxide should be provided. In those tents employing ice for cooling and soda lime for absorption of carbon dioxide the containers for these agents should be insulated. Soda lime is not an efficient absorber unless it is warm.

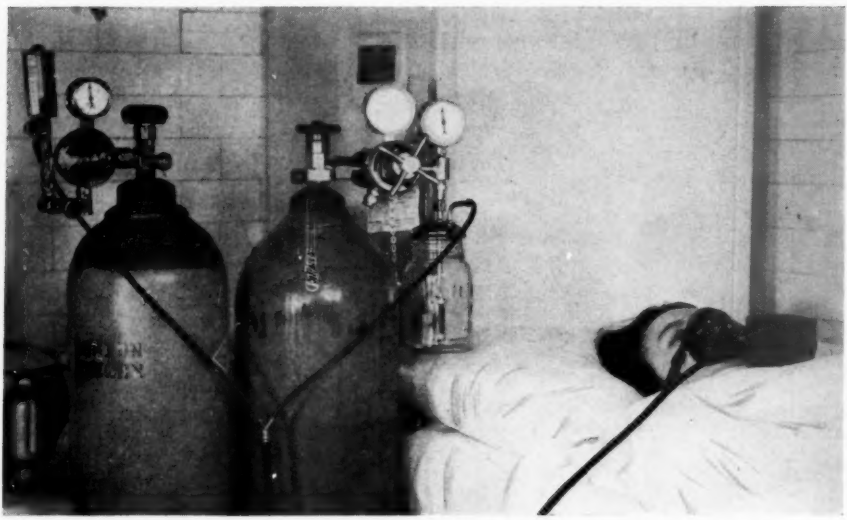

FIG. 2. A mixture of oxygen and helium is being administered to the patient through a B.L.B. mask.

The tent, as it is run in the average hospital, is a most extravagant and inefficient method for the administration of oxygen. Unless the concentration of oxygen and carbon dioxide in a tent is controlled by actual frequent determination, the health of the patient may be jeopardized. A check of the concentration of oxygen in three separate hospitals revealed that the average concentration of oxygen was from 23 to 28 per cent. This low concentration was in most cases the result of leakage of oxygen. The same apparatus when properly supervised was efficient. The oxygen tent, to the average attendant, is only an obstacle which makes the routine care of the patient more difficult. Until attendants are taught the refinements of management and certain special procedures to be employed for those in tents, many patients treated by this method will suffer from anoxemia.

The oxygen chamber gave good results in the experience of many. The chief objections to this type of administration are the expense of installation, the hazard of fire and the limited number of patients who can be treated by this method simultaneously.

OXYGEN IN THE TREATMENT OF DISEASE

Experience has shown that in addition to the primary pathological changes occurring in diseases there are often secondary changes which occur as a result of anoxemia. By relieving the anoxemia the patient is often able to survive until such time as he has developed sufficient resistance to overcome the primary infection. This is the basis for the use of oxygen in the treatment of pneumonia. In order for the cells of the body to live they must receive a sufficient quantity of oxygen but of more importance is the fact that they must receive it at a definite partial pressure. At sea level this partial pressure is approximately 160 mm. of mercury. Any condition which interferes with the maintenance of this partial pressure in the cells produces serious results. In pneumonia the engorgement and consolidation in the lungs result in a decrease in the transfer of gases to and from the blood. At the same time there is a systemic reaction to the changes in the lungs. This is manifested by an increased temperature. For each degree of rise in temperature there is an increase in metabolism (11) of from 5 per cent. to 7 per cent. The anxiety and pleuritic pain experienced by the patient in this stage further increases the metabolism. As the metabolism increases the requirement for food and for oxygen increases. With the requirement for oxygen increased and the supply of oxygen in the blood decreased, the body attempts to stabilize itself by increasing cardiac output.

In the production of energy dextrose is converted into lactic acid. Oxygen is required for this conversion as well as for re-conversion of four fifths of the lactic acid into dextrose. The fifth part of lactic acid remaining is united with oxygen to form carbon dioxide and water. With a depletion of oxygen, as is found in pneumonia, this process is inhibited. Hence there is a collection of lactic acid in the cells. The cells cannot assimilate food because of the acidosis and the acidosis cannot be relieved without oxygen. Consequently the demand for oxygen increases as the supply of oxygen decreases. A constantly increasing demand is made upon the heart whose cells are reacting similarly to those of other parts of the body. Therefore, a pneumonic condition consists of three factors, namely: infection by pneumococci or other bacteria, intoxication, and cellular malnutrition. Recognition of these factors is of utmost importance because the intoxication and cellular malnutrition may be prevented by the early and the adequate administration of oxygen. Once these conditions have become established, oxygen therapy will not always correct them. Lack of oxygen exists long before the first sign of cyanosis appears. Cyanosis of the fingers tips and lips that can just be seen represents desaturation of oxygen to the extent of ten per cent. When cyanosis is definite it represents a desaturation of fifteen per cent., and when it is marked it indicates a desaturation of twenty per cent. The chief factors which

may operate to produce anoxemia are: failure of adequate ventilation as a result of rapid shallow breathing, intrinsic alveolar disturbance, intrinsic changes in the circulating blood, and intrinsic disturbance of cellular tissue (14). Although all these play a part, the essential factors are those which retard access of oxygen to the blood in the pulmonary area.

Considerable diversity of opinion exists concerning the proper safe and beneficial concentrations of oxygen which patients should receive. It is generally agreed that a concentration of under thirty per cent. is of no appreciable value. Barach (15) has stated that a concentration of over seventy per cent. for longer than four days has harmful effects. Karsner (16) has shown that with laboratory animals concentrations of over eighty per cent. result in definite cardiac damage, fibrinous pneumonia, cloudy swelling and congestion of the other organs of the body. Beecher (17) in summarizing the work of Shaw, Behnke and others states that pure oxygen at a pressure of one atmosphere can be breathed by man for about six hours before toxic organic effects are seen. Some of these effects are impaired vision, peripheral constriction, abrupt rise of systolic and diastolic blood pressures, pulmonary edema, extreme pallor, dizziness, a feeling of impending collapse, slowed mental responses, and convulsions. However, Evans (18) contends that anoxemic subjects react differently than normal subjects and that the higher concentrations of oxygen are beneficial in these cases. He followed carefully the course of 409 patients who received oxygen in high concentrations over various intervals of time, and concluded that 100 per cent. oxygen can be given not only without harmful effects to the patient but with excellent therapeutic results. Treatment with oxygen should be started as soon as diagnosis of pneumonia is made and continued throughout the course of the disease. Oxygen should be administered in concentration sufficient to abolish unsaturation of oxygen in arterial blood at all times. The efficacy of oxygen in the treatment of pneumonia is practically in direct proportion to the day of the disease on which treatment is begun.

The pulse rate is the most reliable criterion by which the benefit or failure of therapy of oxygen can be judged. Although numerous other changes are seen, a reduction of the pulse rate is the only factor in the metabolism of man which shows consistent change following exposure to oxygen-rich atmospheres. According to Barach (19) the symptoms of pneumonia may be classified according to their possible mode of origin. The manifestations that are pulmonary in origin are: cough, sputum, pleuritic pain, expiratory grunt, edema of lungs, and shallow breathing. Those that are of toxic origin are: delirium, weakness, rapid pulse, rapid breathing, chill, fever, dyspnea, prostration, and jaundice. The presence of headache, nausea, vomiting, delirium, weakness, rapid pulse, and rapid breathing is indicative of existing toxicity and anoxemia. Of these symptoms, the outstanding ones are those

pertaining to respiratory difficulty. If the respiratory difficulty can be relieved by the administration of oxygen, the patient does not become exhausted and his ability to combat toxemia and bacterial invasion is thereby increased. Discussion of the role of specific chemiotherapy used in conjunction with oxygen therapy is beyond the scope of this paper.

CARDIAC DISEASE

It has been found that the normal saturation of arterial blood was from 95 per cent. to 98 per cent. and of venous blood from 65 per cent. to 75 per cent. In cases of cardiac insufficiency Barach (5) found the arterial oxygen saturation to be between 95 per cent. and 75 per cent. and the venous oxygen saturation to be from 65 per cent. to 30 per cent. Cardiac conditions in which oxygen has been helpful may be divided into four groups, namely: congestive heart failure due to primary cardiac disease, cardiac insufficiency as a sequel to chronic pulmonary disease, acute coronary thrombosis, and coronary arteriosclerosis with chronic cardiac pain. The physiologic action of oxygen in the treatment of cardiac conditions has not been fully explained but various investigators have demonstrated definite changes following its use. In congestive heart failure due to primary cardiac disease it has been found (20) that by using oxygen in a concentration of 45 per cent. there was a relief of dyspnea, diuresis was promoted, edema was reduced, and there was a marked rise in the content of carbon dioxide in the arterial blood. Other changes noted were increase in arterial saturation with oxygen, decreased pulmonary ventilation, decrease in pulse rate, decrease in lactic acid in the blood, and diminution of cyanosis. Similar results were encountered when oxygen was used in cases of cardiac insufficiency which developed as a sequel to chronic pulmonary disease. Oxygen therapy, however, had no influence on the pulmonary disease. The syndrome seen in acute coronary thrombosis is one of acute lack of oxygen due to myocardial insufficiency. Wiggers (21), Ulrich (22), and Barach (20) are of the opinion that the pain experienced in acute coronary thrombosis is a result of an ischemia of the cardiac musculature which can often be relieved by the administration of oxygen. Barach and Levy (23) noted these results following oxygen therapy in acute coronary occlusion: relief of pain and restlessness, improvement in volume of the pulse with slowing and strengthening of cardiac contraction, decrease in pulmonary congestion, lowering of temperature, improvement in respiration, and increase in arterial pressure with decrease in venous pressure. Similar improvement was noted when patients suffering from coronary arteriosclerosis were treated with oxygen. As a therapeutic agent in cardiac diseases, oxygen is of more value in those who exhibit acute anoxemia. Cases of chronic cardiac disturbance such as those showing congenital defects apparently develop a compensatory mechanism which enables them to

withstand their deficiency of oxygen without serious embarassment unless an infective process develops.

In summarizing it may be stated that oxygen has a definite though limited place in the treatment of cardiac disease. It is especially indicated in acute forms. It should not be used as a substitute for other accepted methods of treatment but it should be considered as an aid which will support the circulation until the heart has at least partially recovered. Even in the cases in which recovery is doubtful, oxygen is often warranted for the symptomatic relief which it affords the patient. Administration by means of an intranasal catheter is usually the most satisfactory method, but the B.L.B. mask may be employed to advantage for those exhibiting marked cyanosis.

RESUSCITATION

The Bureau of Vital Statistics, New York City, for the years 1931 and 1934 reports a total of 6110 deaths due to general asphyxia as compared to 2443 deaths from automobile accidents during the same two years. The Division of Vital Statistics, Bureau of Census, reported 18,432 suicidal and accidental deaths from asphyxia occurring in the United States in 1933. Through increased knowledge of preventative medicine and therapeutics, the death rate from many diseases is decreasing. However, as living conditions become more complex the possibility of death from some form of asphyxia increases. Conditions producing asphyxia usually occur without warning and unless proper treatment is immediately instituted, death is certain.

Many communities maintain rescue squads whose duty it is to be prepared at all times to meet asphyxial emergencies. Their work has been very commendable and society owes them a debt for the saving of many lives annually. The same degree of preparedness is not maintained in many hospitals. The one institution where the asphyxiated patient should have the best chance of survival is too frequently poorly equipped. Various machines are relied upon as the sole resuscitating agent. When the emergency occurs the machine may be loaded with empty tanks or it is so well stored that it cannot be found for a time, and there may be no one at hand who is sufficiently skilled in the operation of the machine to make its application efficient. The reason for this situation is that resuscitation has not been definitely recognized as a specialized procedure and hence no one has been made responsible for the purchase, care, maintenance, and operation of proper equipment. Because of the close correlation between the two fields of endeavor, it seems a wise arrangement to make members of the department of anesthesia of a hospital responsible for the maintenance and operation of apparatus used for resuscitation. Workers in different specialties may have their own ideas regarding the treatment of asphyxia. The internist may rely chiefly on stimulating drugs and manual methods of artificial respiration, the surgeon may advocate a

tracheotomy while the obstetrician may suggest tubbing and external stimulation. All of these procedures have their place in the treatment of asphyxia, but none alone is sufficiently comprehensive. Resuscitation should become the duty of a specialist who makes a study of the processes involved and who is able to apply all forms of treatment as they are indicated.

Asphyxia may be induced by a wide variety of causes. Regardless of the cause, the events which follow are similar. The problem of resuscitation therefore resolves itself into one of promptly breaking the vicious circle by relieving cellular anoxia. If it cannot be broken before the damage becomes irreversible, the patient will die. Patients, in whom resuscitation has apparently been successful but only after some delay, may die within a short time as a result of these irreversible changes.

Coryllos (24) has classified asphyxia according to degree into slight, moderate and severe. Anesthetists are familiar with the signs and symptoms of the severe and moderate phases but it is the manifestations of slight degrees of asphyxia with which we must be familiar because, if unrecognized and untreated, patients will progress toward the more severe stages of the syndrome. In slight asphyxia the symptoms often resemble those following an overdose of alcohol. There may be headache, depression, apathy, drowsiness or excitement, and a general loss of self control. The subject may become quarrelsome and insolent. He is often reckless in the face of danger and he is quite confident that his mind is clear. Evaluation of time is altered and memory and understanding are impaired. The subject may see without knowing what he sees. Pain is dulled and judgment of position is altered. There is considerable muscular weakness and easy fatigability. Nausea, loss of appetite, and perhaps vomiting may be exhibited. At first, there may be a slight rise in blood pressure with an increase in frequency and apparent force of cardiac contraction. This is due to a stimulation of the vasomotor and cardiac centers of the medulla as a result of anoxia. The increased force of the heart beat later is diminished as the rate further increases. Breathing is increased in rate and may be shallow and periodic in character. The appearance of these symptoms may first manifest themselves several hours after the onset of asphyxia if the asphyxia is mild in degree.

In those conditions in which asphyxia is slow in developing, the body may accustom itself in some degree to the change and in this way compensate for lack of oxygen. This acclimatization is brought about by the kidney, the lung and the blood itself. With the rapid breathing of asphyxia, the carbon dioxide is washed out of the system, and results in an alkalemia (25). The kidney compensates for this by excreting an alkaline urine with a low content of ammonia. The pulmonary volume increases, thinning the alveolar epithelium, and thus permitting a more rapid gaseous exchange. The spleen contracts, the

red marrow proliferates and the value for hemoglobin rises thereby increasing the carrying capacity of the blood for oxygen. The individual under these circumstances may be quite capable of supplying his requirement for oxygen under ordinary conditions. However infection, exertion or any other condition requiring oxygen in excess may overpower this compensatory mechanism and cause rapid, lethal asphyxia.

With the increase in the armamentarium of anesthetic agents now in use, the problem of anesthetic asphyxia increases. Many of the regional anesthetic agents now in use act as convulsants when given in overdose or when accidently introduced into the circulation. The convulsive action of these drugs produces spasm of the respiratory muscles which results in asphyxia. One should therefore administer oxygen under pressure until an anti-convulsant, such as a barbiturate, can be administered to relieve the spasm. Death from the administration of barbiturates may likewise be the result of asphyxia. Two factors are involved. The drug may depress the respiratory center to such an extent that the demand for oxygen by the tissues is not satisfied or the blood pressure may be diminished to the point where the coronary circulation is not sufficient to provide the cardiac musculature with an adequate supply of oxygen. In either case oxygen should be administered under positive pressure until the effects of the drug may be counteracted by a convulsant drug or until the drug is detoxicated. Many untoward effects accompanying spinal anesthesia are the result of anoxia, due to depression of the respiratory center by action of the drug, or it may be associated with stagnation of circulation. In either case the treatment consists of increasing the content of oxygen in the tissues, especially of the brain by administering oxygen by inhalation and fluids intravenously. Since the advent of cyclopropane as an inhalation anesthetic agent, asphyxia during inhalation anesthesia occurs less frequently than formerly. As the use of helium as a diluent becomes more prevalent one may predict that some cases of asphyxia will result from administration of too high concentrations of this agent. Kaye (26) in reviewing a series of 105 anesthetic fatalities concluded that asphyxia from respiratory obstruction was responsible for ten per cent. of the deaths. The treatment of asphyxia from respiratory obstruction is evident: establish an efficient airway and administer oxygen in adequate concentration and under sufficient pressure. The authors believe that the best method of supplying oxygen is through an endotracheal catheter fitted with an inflatable balloon. Sufficient pressure may be employed to rhythmically inflate the lungs without the danger of distending the stomach.

Patients not infrequently arrive in hospital accident rooms in a state of moderate or severe asphyxia. Ruth has (27) outlined a generalized plan of action to be followed by specific treatment, varying with the etiological factor, and by certain supportive measures. All

mechanical interference to normal respiration must first be removed. A foreign body should be removed if that is possible. If removal is delayed, oxygen or oxygen and helium mixtures should be administered under sufficient pressure to force oxygen past the obstruction, if possible, while preparations are being made for a tracheotomy or bronchoschopic removal of the foreign body. Permanent patency of the airway must be assured. An intratracheal tube of large bore may be introduced and fluids aspirated through a smaller catheter inserted through the larger tube. Oxygen may be supplied by mouth-to-mouth or mouth-to-nose insufflation. The accepted manual methods of resuscitation may be employed but mechanical methods are usually more efficient. A mask and a bag (Fig. 3) filled with oxygen may be used

FIG. 3. Positive pressure may be applied intermittently to inflate the lungs.

to inflate intermittently the lungs. If resuscitation must be maintained for some hours, a mechanical resuscitator (McKesson type), providing alternately positive and negative pressure, may be used. If the intratracheal tube to which this type of apparatus is attached is not equipped with an inflatable balloon, a Levine tube should be introduced into the stomach to prevent its distention. If resuscitation must be continued longer than 12 hours, one must consider the necessity of placing the patient in a resuscitator (Emerson or Drinker), providing intermittent negative pressure. Prolonged intubation may be conducive to production of a tracheitis. With the patient in this type of apparatus, the intratracheal tube can usually be removed. If edema

of the larynx develops following the original trauma, a tracheal stoma should be established before the intratracheal tube is removed. If the patient's original injury involves the deep structures of the neck, tongue, or of the pharynx the danger of the subsequent occurrence of emphysema is very real. Mature consideration must be given regarding the advisability of performing a tracheotomy to provide an airway, should this unfortunate complication seem likely to occur. It seems to be a rather radical preventative measure but it has been a life-saving one on occasion.

ASPHYXIA NEONATORUM

Approximately 80,000 infants die annually at birth in this country and 30,000 more die during the first day of life (28). Many of these are respiratory in origin. Henderson (29) states, "If measures to insure expansion of the lungs were as much a part of the routine treatment of the new-born as is now the disinfection of the eyes, lives would be saved as effectively as blindness is now prevented." Asphyxia in the new-born may be divided into four types, namely: asphyxia livida, asphyxia pallida, asphyxia due to intracranial hemorrhage, and asphyxia due to inspiration of foreign material during delivery. Asphyxia livida results from obstruction of the circulation between the child and the placenta or obstruction of the circulation to the child's head. This obstruction usually occurs late in labor and is of short duration. The baby is born with extreme cyanosis evident. If the infant is not deeply narcotized and if the heart is still beating, resuscitation can usually be effected by inhalational methods. Asphyxia pallida is of far more serious import. A baby in this condition exhibits evidences of shock. Respiration is greatly depressed, cardiac contractions are slow and feeble, muscular tonus is lost, circulation fails, and the capillaries and veins of the skin are deficiently supplied. Similar methods in treatment should be applied.

Asphyxia livida and asphyxia pallida develop previous to delivery while asphyxia due to intracranial hemorrhage develops after birth. Babies suffering from asphyxia following intracranial hemorrhage usually breathe at birth but as intracranial pressure is increased due to hemorrhage, respiration gradually fails. Asphyxia due to aspiration exhibits the classical signs of an obstructed airway.

Considerable diversity of opinion has existed concerning the explanation of the initiation of the first gasping inspiration. Normally respiration begins in utero. Snyder and Rosenfeld have confirmed this both experimentally and clinically. Asphyxia of the new born therefore becomes a suppression of a previously existing respiration rather than a failure of a new mechanism to begin its function. The former procedure of rough handling has recently been superceded by more rational methods. Babies suffering from asphyxia are now treated as are individuals in shock. Extreme gentleness is practiced. The cold water

in the tub has been replaced by warm water, thus conserving the body heat. Efforts are made to restore the normal relations between oxygen and carbon dioxide in the centers in the brain and in this way allow the child to breathe rather than produce respiration by force. The first procedure in the resuscitation of the new-born is the establishment of an unobstructed airway. This can usually be done by lowering the head and gently wiping the mucus from the nostrils and pharynx. If the

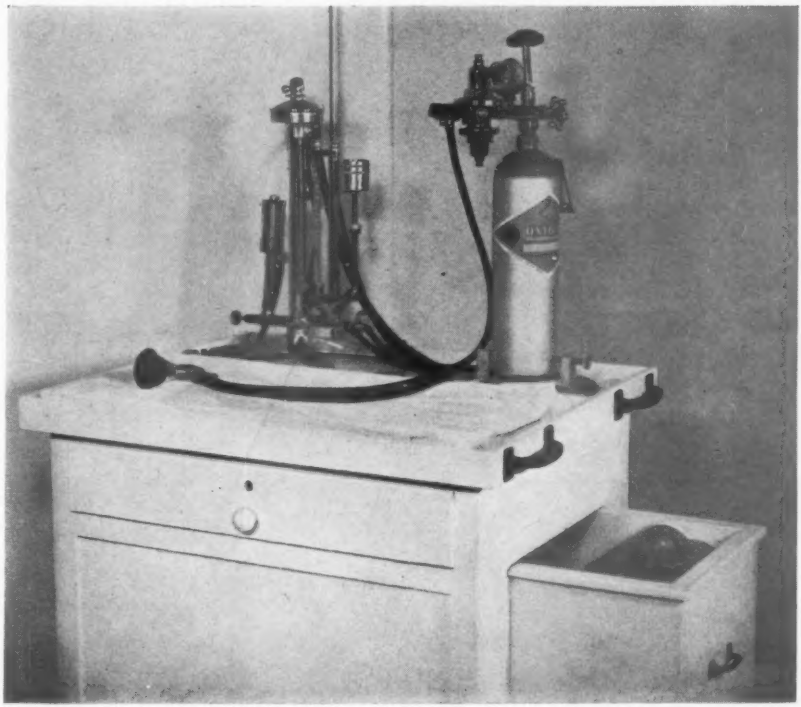

FIG. 4. A resuscitator providing controlled intermittent positive pressure mounted on a convenient stand, equipped with a drawer which may be used as an oxygen chamber for a new born infant.

obstructive material cannot be reached by this means, a catheter may be inserted into the pharynx and the material may be aspirated, or the catheter may be directed into the trachea either manually or with the aid of a laryngoscope and the mucus may be aspirated. The baby then may breathe somewhat inefficiently. In order to help, initiate or aid in this movement it is our practice to employ a mechanical resuscitator (Fig. 4) which provides intermittent controlled positive pressure. If inspiration remains inefficient after it has been initiated the baby is placed in an oxygen chamber. For this purpose the stand on which the resuscitator

is mounted is equipped with a drawer (Fig. 4). This drawer may be removed and placed on top of the table. A mattress, sheet and blanket are constantly kept in this container. The baby is placed in it and an oil silk covering is employed to convert the drawer into an oxygen chamber (Fig. 5). The delivery tube from the constant flow meter of the resuscitator terminates in a perforated rubber stopper. This rubber stopper is inserted in a hole in the side of the oxygen chamber. With a flow of five liters per minute, the baby may be maintained in an atmos-

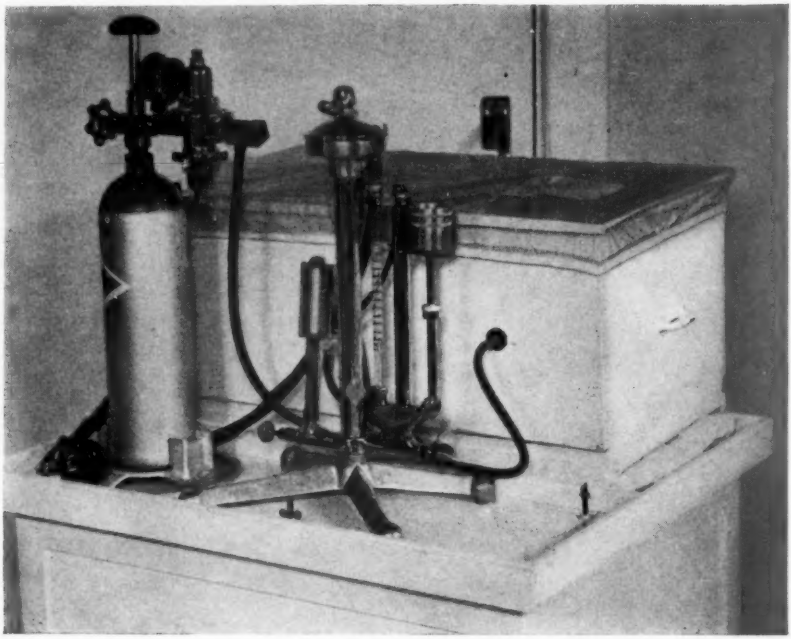

FIG. 5. Following primary resuscitation of the infant, he may be placed in this type of oxygen chamber temporarily.

phere containing 60 to 80 per cent. oxygen. When the infant's condition warrants it, the perforated rubber stopper may be replaced by a solid rubber stopper and the oxygen chamber may be carried to the nursery where the infant is transferred to a Hess bed that can be readily converted into an oxygen chamber (Fig. 6). This oxygen chamber offers the added advantage of having the temperature thermostatically controlled. The infant may be kept in this chamber until it is considered safe to remove him to an ordinary crib. We are confident that this type of treatment has been responsible for a reduction in the mortality rate of infants, particularly those classified as prematures.

Final Summary.—Problems in oxygen therapy and resuscitation are of vital interest to the anesthetist. A thoroughgoing understanding of

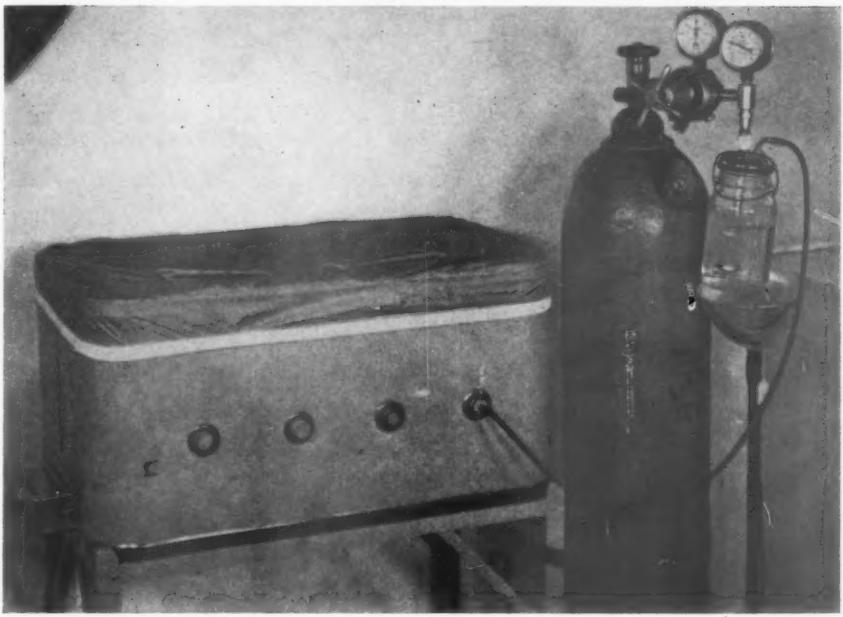

FIG. 6. A Hess bed may be readily converted into a satisfactory oxygen chamber, thus providing an adequate concentration of humidified oxygen. The temperature of the chamber is thermostatically controlled.

the fundamentals involved is an essential requirement for successful treatment. Certain fairly well standardized methods have been developed. If they are employed wisely, one's percentage of successes should be fairly high. Ideal methods have not been achieved, however, and further investigation of these problems is warranted.

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A Section on Anesthesiology will be held in the Scientific Assembly of the American Medical Association in Cleveland, Ohio in June, 1941.

DURATION OF LOCAL ANESTHESIA IN RELATION TO CONCENTRATIONS OF PROCAINE AND EPINEPHRINE

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In order to achieve a prolongation of local anesthesia, addition of epinephrine has been recommended (1) and used extensively. However, few exact experiments have been made to determine the optimal concentration of procaine and epinephrine necessary for a certain duration of local anesthesia.

Procaine.—From previous experiments (2), in which anesthesia was tested on the rabbit's cornea after subconjunctival injection of procaine HCl, it was concluded that the optimal amount of fluid has to be adapted according to size and type of the injected area; an increase beyond this optimum does not increase the depth or prolong duration of anesthesia to any noteworthy degree. The duration of anesthesia with procaine HCl was found to be only slightly increased by increasing the concentration of the drug above 1 per cent. Figure 1 shows that a tenfold increase (from log. — 3 to log. — 2) results only in a prolongation from about 36 to 64 minutes. The practicability of increasing the concentration is still more restricted by the toxicity of procaine which is known to increase in geometrical ratio to its concentration (3). Thus, about 200 cc. of a ½ per cent. solution of procaine HCl can be used for infiltration anesthesia, 80 cc. of 1 per cent., 20 cc. of 2 per cent., and only 5 cc. of 4 per cent. The corresponding absolute amounts of procaine are 1.0, 0.8, 0.4, and 0.2 grams respectively.

Procaine and Epinephrine.—Although causing local anemia and prolonging anesthesia, epinephrine may increase the dangers of anesthesia, at the site of injection, e.g. causing ischemic gangrene of the fingers, and systemically in vasolabile and hyperthyroid patients, or through accidental intravenous injection (4). It, therefore, seemed important to study the effect of different concentrations on duration in order to be able to reduce the amount of epinephrine to the lowest possible level. Figure 2 shows the effect of different concentrations of epinephrine added to 1 per cent. procaine HCl. The solution was injected under the conjunctiva of the rabbit's eye and the resulting anesthesia of the cornea tested with the help of an electric inductorium. Epinephrine 1:1,000,000 showed no prolongation, 1:400,000 an average of 40 per cent. prolongation, and 1:200,000 60 per cent. prolongation (to 91 minutes), concentrations above 1:200,000 increased the duration of anesthesia only to a very small extent; 1:50,000 gave an average duration of 98 minutes.

Occasionally these higher concentrations caused reactive hyperemia and edema of the conjunctiva, or failure of return to the normal sensitivity of the cornea within the next few hours; these symptoms have to be considered as signs of damage to the tissue. Bieter (5), using ⅛ per cent. procaine HCl in the human wheal test, obtained comparable results; his value for duration of anesthesia with ⅛ per cent. procaine is 16.6 minutes; after addition of epinephrine 1:500,000 = 65.4 min.,

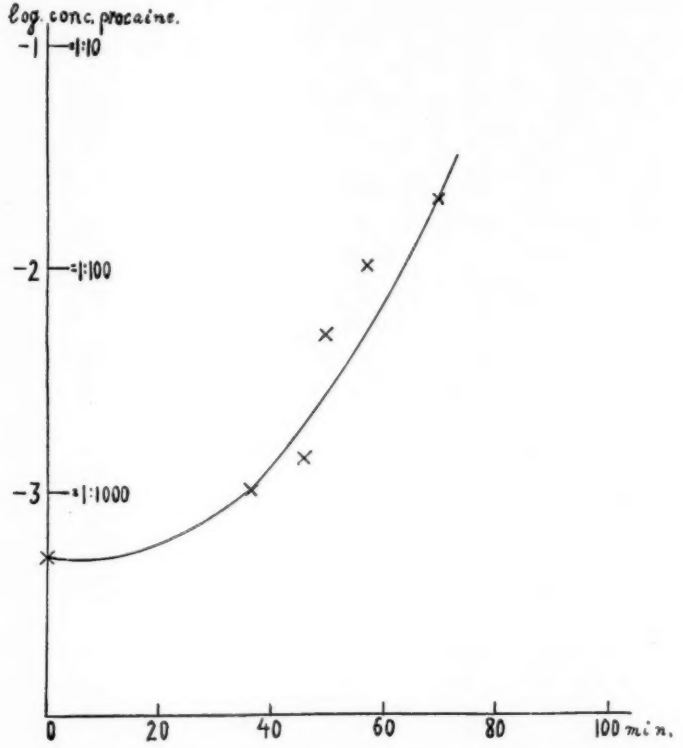

FIG. 1. Concentration-duration curve for injected procaine HCl. Fluid volume constant (0.8 cc.). Abscissa: duration of anesthesia in minutes. Ordinate: logarithm of concentration per cent. Total number of experiments 88.

1:200,000 = 89.2 min., 1:100,000 = 87.2 min., 1:50,000 = 83.0 min. Thus no further prolongation could be obtained by increasing the concentration beyond 1:200,000; he reported similar results for Metycaine, Cocaine, and Panthesine.

Summary.—Increasing the concentration of procaine beyond 1 per cent. results in a prolongation of anesthesia proportional to a simple multiple of the logarithm of concentration.

Epinephrine 1: 200,000 prolongs anesthesia with 1 per cent. procaine HCl by about 60 per cent.; lower concentrations are less, higher are slightly more effective, but the latter may cause damage to the tissue.

The author is indebted to Dr. C. H. Thienes for many valuable suggestions.

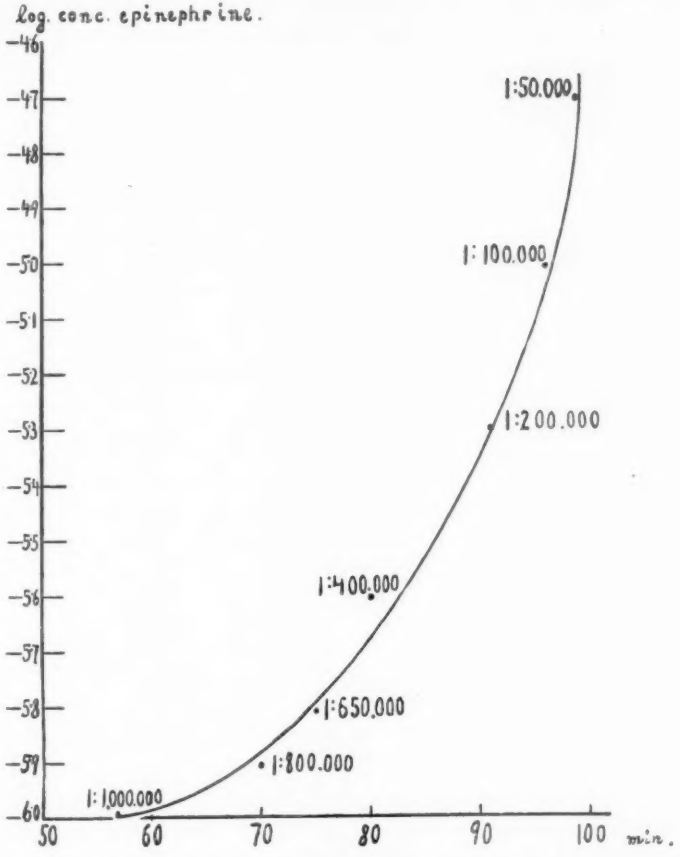

FIG. 2. Concentration-duration curve for injected procaine HCl and epinephrine HCl. Procaine HCl concentration constant 1 per cent. Fluid volume constant (0.8 cc.) Abscissa: duration of anesthesia in minutes. Ordinate: logarithm of concentration of epinephrine HCl. Total number of experiments 37.*

* This and the preceding graph are based on arithmetic averages. The deviation from the mean was within ± 30 per cent.

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HYPERTHERMIA FOLLOWING ANESTHESIA

A Consideration of Control of Body Temperature During Anesthesia

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Two instances of deranged temperature regulation developed on our service almost simultaneously. Another had been observed previously. These cases, together with one that had been observed elsewhere by a member of the department, furnish the basis for this report. Subsequently frequent records of temperature taken during anesthesia showed numerous moderate elevations. The great majority of these thermal changes were unimportant. They nevertheless indicate that ether anesthesia, contrary to the opinion widely held, does not frequently lower body temperature in humans, at least under conditions of modern surgery. These frequent moderate elevations of temperature and the reports of high temperatures encountered in our study suggest that under propitious conditions the factors working toward disturbance of thermal control during anesthesia become accentuated. They would continue then to act until an elevation of considerable and possibly dangerous magnitude developed. In other words, these instances of severe hyperthermia probably represent the unusual end result of a development which ordinarily barely gets under way, or at best achieves only moderate proportions.

Excessive hyperthermia seems to occur mostly after ether anesthesia, and then very infrequently. [See Gibson (1).] However, it appears to be limited chiefly to young children and occurs during hot weather. High temperatures are produced which approach the critical levels around one hundred and eight degrees. The rise in temperature is accompanied by a remarkable elevation of pulse and respiratory rates. A fatal termination may occur.

The condition is due, probably, to simultaneous disturbances of all three phases of regulation of body temperature, namely, (1) heat production, (2) heat loss and (3) integration of the activities of the central nervous system related to temperature regulation.

Three Factors Control Body Temperature

1. *Heat Production.*—Combustion in the tissues is the source of heat produced by the body. Activity of the skeletal muscles is the greatest single factor. A much less important source lies in the metabolic activity taking place in the liver and kidney, and in the cardiac

muscle. The rate of combustion of a given tissue may be increased by the action of products of internal glandular secretion, such as epinephrine (2) and possibly thyroxine.

2. *Heat Loss.*—Heat loss is accomplished by the physical processes of radiation, convection and vaporization. The relative importance of these factors has been studied in detail by Du Bois (3). Heat loss through vaporization occurs from the lungs as well as from the skin. Vaporization, relatively unimportant under normal circumstances of temperature and clothing, assumes greatest importance in distribution of heat during a sharp rise of external temperature.

3. *Integration Within the Central Nervous System.*—The physiological mechanisms through which the physical factors of radiation, convection, vaporization and combustion are influenced are numerous. They function through such varied activities as (*a*) dilatation and constriction of the cutaneous vessels, (*b*) the activity of the sweat glands, (*c*) piloerection, (*d*) pulmonary ventilation, (*e*) output of epinephrine and (*f*) voluntary and involuntary activity of the skeletal muscles.

In turn, the adequate integration of the activities of these complex processes to the end of maintaining a balance between heat production and loss requires continuous control by the central nervous system. These connections within the central nervous system are widespread. They involve special cutaneous sense receptors of remarkable sensitivity (4), afferent tracts in the cord and brain stem, hypothalamic and cerebral integration of impulses and efferent discharges over somatic, sympathetic and parasympathetic pathways. The control of this diverse activity within the nervous system is centered in the hypothalamus.

There is no longer any doubt that abnormalities of heat regulation develop subsequent to lesions at the base of the brain involving the hypothalamus. Specific subdivisions of the hypothalamus control separately heat production and heat distribution (5, 6).

HEAT REGULATION DURING ANESTHESIA

In hot weather dispersion of heat is accomplished with difficulty, especially in children. Radiation and convection from the skin ordinarily account for the largest part of the heat loss. On hot humid days, when the atmospheric temperature approaches the body temperature, the effectiveness of these mechanisms is curtailed. Vaporization from the skin then becomes the chief means of cooling the body.

During anesthesia vaporization meets certain man-made impediments. Custom has decreed that patients be completely draped during operation regardless of atmospheric conditions. As a result not only are convection and radiation made more difficult, but vaporization can become really effective only after perspiration has moistened at least two layers of overlying sheets. The output of perspiration of a small child may be insufficient to do this.

Furthermore, vaporization from the skin of the face, which is ordinarily highly effective, and from the lungs is impaired by the presence of the anesthetic mask and the anesthetist's arm. This may be partially counteracted by the cooling effect of vaporization of ether.

On the other hand, as an effect of the administration of ether, production of heat may be held stable or will be slightly increased. The administration of ether is associated with a marked adrenergic response on the part of the organism (7). This is the probable result of the response of a defensive mechanism to irritation of the respiratory tract and to changes in the central nervous system initiated by approaching loss of consciousness. This response to ether is shown in the behavior of the eye, the blood sugar, the liver glycogen, the small intestine, the spleen and the behavior of the intact circulation (as contrasted to the effect of ether on isolated heart muscle). The epinephrine secreted internally increases tissue metabolism and heat production. Secretion of the thyroid gland, too, may be increased through an ultimate effect of an original adrenergic response, although the thyroid gland is not usually considered as subject to sufficiently rapid changes of activity to have a part in regulation of the temperature of the body (8).

This total effect on elevation of temperature would be trivial compared to the ordinary capacity of the body for regulation. It achieves significance only through the coexisting impairment of heat distribution.

Added to this, the control of the central nervous system exerted on the widespread activities related to heat regulation may be faulty. Heat regulation in infants and small children is notoriously erratic. This may be related to the immature development of the central nervous system or of certain tracts within the system. Increased strain is placed on the regulating mechanism, probably because of a disproportion between body weight and body surface, and of the elevated rate of oxidation of resting tissue in children. Further, direct depression of excitability and conductivity results from the action of narcotic drugs upon nervous tissue. This, at least, has been shown as a direct effect of relatively high concentrations on isolated nervous tissue (9).

These considerations show that during ether anesthesia the three mechanisms of heat control by the body can become affected. As a result of the internal secretion of epinephrine, and possibly thyroxine, the rate of combustion of tissue is elevated. This latter factor possibly is aided by struggling during induction. A small but uncompensated rise of temperature takes place. The rise is uncompensated for reasons examined previously in detail and concerned with impaired radiation, convection, vaporization and control exerted by central nervous system.

This comparatively trivial rise starts in motion another chain of events. For each rise of one degree F. in body temperature, an increase of seven per cent in the basal metabolic rate occurs. This in turn adds to the production of heat which is already uncompensated.

Thus the basis of a vicious cycle producing a continuous rise in the temperature of the body is established: increased heat causing increased metabolism and increased metabolism producing increased heat. In its later stages the progression within the cycle would be expected to speed up, as did happen in Cases one and two. This continues until the cycle is broken. Otherwise high temperatures are attained that produce either permanent damage to the central nervous system or death.

It is interesting to contrast the mechanism of this cycle, where a minor and otherwise negligible temperature rise goes on to a serious termination, with the enormous production of heat that is effectively disseminated by the body during violent muscular exertion. In the latter instance, for example following the exertion of an athlete during a mile run, the temperature may rise rapidly because the mechanism of heat distribution, though working, is temporarily overwhelmed by the extraordinary metabolism taking place in the largest skeletal muscles. The elevation of temperature is rapidly brought under control on cessation of the muscular activity.

CASE REPORTS

The following cases of hyperthermia following ether anesthesia have been personally observed.

Case 1: C. F., an under-developed, Puerto Rican baby 22 months old, was prepared for a plastic operation on her face to remove a large nevus covering the nose, lower lid and cheek. This patient had had two previous operations related to the same condition. One was followed by an immediate rectal temperature of one hundred and six degrees which returned to normal in six days. The anesthetic agents used were ethyl chloride for induction followed by the administration of ether. On the day of operation the official temperature reported by the U. S. Weather Bureau was ninety degrees during part of the procedure.

The operation had been in progress about two hours during which time a gradual rise in pulse and respiratory rates was noticed. The patient's condition was not considered dangerous. Shortly thereafter the child's condition became rapidly critical, with a pulse rate approaching two hundred and a high temperature of the skin. A rectal temperature showed an elevation to one hundred and seven degrees. Despite attempted restorative treatment the pulse and respirations failed rapidly; and death occurred within twenty minutes of the time the condition was first regarded as critical.

The medical examiner regarded the case as one of heat prostration and no autopsy was done.

Case 2: L. R., a Puerto Rican girl, aged 2 years and 8 months, weighing thirty-eight pounds, was subjected to an uneventful tonsillectomy and adenoidectomy at 3:20 P.M. The afternoon temperature was eighty-four degrees (U. S. Weather Bureau). She returned to the ward shortly before 4 P.M.

Late that afternoon she bled a moderate amount. She was anesthetized again at 8:15 P.M., and the bleeding point was ligated. An infusion of approximately 1200 cc. dextrose in 5.0 per cent. solution in normal saline was given during the next two and one-half hours. In both instances open ether anesthesia followed by pharyngeal insufflation of ether, with a fifteen second induction with ethyl chloride, was used. At 11:20 P.M. only partial recovery from the anes-

thesia had occurred. The temperature then, the first recorded following operation, was one hundred five and two-fifths degrees; and by midnight this had risen to one hundred seven and two-fifths degrees. The child continued in a stupor. A pulse rate of two hundred and respirations at seventy per minute accompanied the fever. At 3:30 A.M. a muscular reaction, interpreted by the nurse as a mild convulsion, occurred and was repeated twice during the night. The child remained stuporous for thirty-six hours.

During the first twenty-four hours, active measures for reducing her temperature were used. Despite this the temperature on several occasions rose above one hundred and six degrees. The pulse rate averaged two hundred, and the respiratory rate was above sixty, with peaks of seventy-two and seventy-eight.

The condition cleared by lysis, with the child gradually becoming mentally clear over a period of several days. The temperature returned to normal on the eleventh day. All laboratory and X-Ray findings were essentially normal beyond the development of a moderate anemia. No residual cerebral effects were found on follow-up visits.

The use of an intravenous infusion of 1200 cc. of dextrose in 5.0 per cent solution in normal saline was at first considered a complicating factor. The Pediatric Department ordered and administered this medication. In view of the loss of blood fluid loss from perspiration, and hemoconcentration following the administration of two ether anesthetics (10), the amount was not excessive and probably was not the cause of the unusual postoperative course. In fact, after considering a very similar case with a fatal termination, the opinion could be defended that this vigorous early attack on dehydration saved the child's life.

At this point it is of interest to record a case observed by one of the members of our staff at another institution. Like the instance just recorded, this patient was a child operated on during a hot summer day for tonsillectomy. The temperature continued rising during the day and reached one hundred and seven at about midnight. The child died shortly afterward.

Twelve days after this occurrence, the department was asked to prepare the patient described in Case 3 for anesthesia. The possibility of the development of hyperthermia was recognized because of the existence of a combination of factors related to dysfunction of temperature regulation. These were (1) the continued hot weather (11), (2) a young and under-developed child, (3) ether anesthesia of long duration, and (4) the nature of the draping that would leave only a hand exposed.

Because of these factors the temperature of this child was checked frequently throughout the operation. This was the first of many observations made subsequently, and was done conveniently by taking axillary readings.

Case 3: D. B., age 3 years and 3 months, weighing only twenty-seven pounds, was prepared for a plastic operation for contractures of the skin of the hand, fingers, wrist and forearms that followed a burn. Dissection of the scar with repair by a split graft from the abdomen was contemplated. The operation was expected to require about three hours.

Making allowance for the disproportion between the child's age and weight 100 mgs. of tribromoethanol in amylene hydrate per Kg. were given thirty-five minutes before induction of ether anesthesia. This put the child to sleep, but during the administration of ether vapor moderate struggling occurred.

The official temperature reported by the Weather Bureau at one time during this procedure, was eighty-eight degrees.

The course of this anesthesia was marked by (1) remarkable and early elevation of pulse and respiratory rates which progressed eventually to two hundred and twenty and seventy-two respectively and (2) the development of a rise of axillary temperature to one hundred four and one-fifth degrees. This is probably equivalent to more than one hundred and five degrees by rectum. The rectal temperature directly following the completion of the operation was one hundred four and three-fifths degrees.

During the operation the temperature continued to rise, but at a slower rate, even after the tendency toward elevation had been noted and more skin had been exposed to help control the condition. It was not until the end of the operation, with the cessation of ether anesthesia carried at the lightest possible plane (the patient moved her limbs several times during the last one and one-half hours) and after removal of all drapes, that the temperature began to fall.

The child awoke within fifteen minutes, was restless and shortly complained of feeling cold. The temperature then (one-half hour post-operatively) was one hundred three and one-fifth degrees and had fallen rapidly from the one hundred four and three-fifths degrees recorded about twenty minutes previously. The pulse rate remained at two hundred and the respiratory rate fifty-two. The temperature dropped to one hundred and four-fifths (rectal) three hours after the termination of the operation. It was normal during the first and subsequent post-operative days. The child was subsequently anesthetized with avertin and ether for one-half hour, ten days later, without incident.

Despite the remarkably rapid pulse rate that developed early in the operation, the operation was not discontinued because it was thought at that stage that the entire hand would be jeopardized. The general condition throughout appeared better than specific clinical findings would indicate. The pulse was always precisely countable, despite the extremely rapid rate.

This case in its inception, progress and subsequent course appears to be explainable only on the basis of deranged temperature regulation resulting from the conditions surrounding the operative procedure and anesthesia.

DISCUSSION

In order to estimate the incidence and direction of changes in temperature during operations lasting three quarters of an hour or more and anesthesia with many techniques and agents being employed, fifty consecutive patients were observed. Axillary readings were taken when the anesthesia was induced and at frequent intervals throughout the operation. They were made during winter weather under ordinary operating room conditions. Results are shown in Table 1.

The significance of this table, showing a high incidence of elevation of temperature, is of some importance in view of the previous discussion and the assertion in standard works on pharmacology that anesthesia lowers body temperature. Though the minor elevations noted

TABLE 1

TEMPERATURE CHANGES DURING ANESTHESIA OF 45 MINUTES OR LONGER

50 Cases *		
Elevation		33
No Change		14
Fall		3
33 Elevations		
Less than 1 degree F.		20
1–1½ degrees		8
2–3 degrees		5
* Ether	open	1
	closed	33
	colonic	1
Nitrous Oxide	closed	7
Cyclopropane	closed	4
Pontocaine	spinal	1
Pentothal Sodium	intravenous	1
Metycaine	transsacral	1
Avertin (alone)	colonic	1
		50

are probably no greater than changes developing in the normal individual not under anesthesia, the occasional elevations of two degrees or more are well beyond the normal range for individuals at rest over a comparable period of time.

In this series of fifty cases the highest elevation noted was an even three degrees. The patient was a child 2.5 years of age, mentally deficient, subjected to two and one-half hours of anesthesia for syndactylism.

During the period of closely observing effects related to control of temperature occasional developments of interest have been noted. In one instance, in a patient under spinal anesthesia, the axillary temperature fell to ninety-seven and shivering developed. The shivering was feeble and was confined to the upper extremity where anesthesia was not present. Sherrington (12) originally observed that the shivering reaction indicated with great accuracy the level of an experimental lesion of the cord in animals. Shivering fails to occur below the lesion. This same effect is apparently obtained after establishment of the temporary lesion of spinal anesthesia in man.

Further it was found that on infrequent occasions temperatures of the face exceeded axillary temperatures. In one instance the difference was one and two-fifths degrees. The difference was probably enough to make the temperature of the face higher than the rectal temperature. The face was dry, hot and red during these periods. This unusual effect suggests that under certain circumstances during anesthesia a more marked redistribution of blood must take place than is generally realized (10, 13). Du Bois (3) has stated that it is possible for the cutaneous temperature to exceed rectal temperature under certain conditions during the period of heat loss after a chill.

The condition of hyperthermia is of rare enough occurrence scarcely to cause concern about its prevention. However when infants and children are scheduled for prolonged operations under ether anesthesia during the hot summer weather, the possibility of this development should be considered during the preoperative preparation. Axillary temperatures easily taken and made a part of the anesthesia record might provide a timely warning.

SUMMARY

The physiological mechanism through which heat regulation is accomplished has been briefly considered. Conditions existing during anesthesia and operation have been shown to be able to impair, under selected circumstances, each of these mechanisms. Three cases of excessive elevation of temperature during anesthesia have been discussed. Further, it has been shown that temperature readings taken routinely during operation reveal frequent slight elevations and an occasional distinct rise. Other observations related to control of body temperature during anesthesia have been mentioned.

These findings suggest that severe hyperthermia occurring rarely, accompanying and following operative procedures and anesthesia, depends for its development upon a chance simultaneous impairment of all phases of control of temperature. The specific rise in temperature that develops is accompanied by an equally characteristic elevation of the pulse and respiratory rates.

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ENDOTRACHEAL NITROUS OXID ANESTHESIA FOR TONSILLECTOMY;

REPORT OF 1,550 CASES*

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The anesthetic problem in tonsillectomy receives very little attention when one considers the importance of the subject. It has been estimated by the United States Public Health Service that over a million and a quarter tonsillectomies are done every year in the United States. This is by far our commonest operation, is practically always elective, and is carried out on patients whose general health is good. It is usually considered a minor procedure to be performed in the office of the general practitioner. One cannot help but be shocked, therefore, to realize the frequency with which fatality follows this operation and these fatalities are due to poor anesthesia in the large majority of cases. Every year not one but several deaths occur in our community, which is probably no worse than the average for the whole country. There can be no doubt that most of these could be prevented by better anesthesia.

The morbidity and mortality produced by the anesthesia is out of all proportion to the importance of the operation. The administration of anesthesia for tonsillectomy is one of the most difficult in the routine of our work, yet how often do we see that responsibility delegated to the most junior intern or even medical student?

Difficulties

Asphyxia.—Obstruction to respiration is certainly the commonest and most serious complication of anesthesia, and is especially apt to occur during this operation. The position of the patient that is commonly used, involving as it does hyperextension of the neck is not conducive to free respiration. The widely open mouth often causes serious respiratory embarrassment, for the soft tissues of the floor of the oral cavity are apt to be pushed back into the throat. Careless use of the tongue depressor must be guarded against, lest asphyxia be produced. Foreign material in the throat such as mucus, blood, sponges or even particles of tonsils or adenoids may interfere with the free exchange of air. It is impossible to over-emphasize the importance of a

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free airway, for nothing can produce such serious symptoms as acute asphyxia.

Aspiration.—In no operation is the hazard of aspiration so real, and everyone has seen cases of pneumonia and pulmonary abscess following tonsillectomy. Local anesthesia does not prevent this complication. The principal causative factors are prolonged deep anesthesia with paralysis of the bronchial cilia, poor position of the patient, and a faulty technic that allows excess blood to collect in the throat. Post-operative bronchoscopies show that there is some aspiration in nearly every tonsillectomy, but that the amount of blood seen increases in direct ratio to the depth of the anesthesia. Post-operative pulmonary abscess and aspiration pneumonia are serious complications producing prolonged disability and a high mortality.

YOUTH OF PATIENTS

There is no doubt that local anesthesia removes much of the danger of asphyxia and aspiration, but as the great majority of our patients are children it is usually not feasible. The child is, however, a relatively poor risk for general anesthesia as it is easy to overdose him with the agent and generally more difficult to maintain an even plane, for due to the small volume of the circulation, variations in depth of anesthesia occur much more rapidly than with the larger adult. Enlarged tonsils and adenoids, more common in children, increase the dangers of respiratory obstruction.

Children are usually more nervous and noncooperative than adults, and this considerably increases the risk and difficulties of induction. It is regrettable that the introduction of most individuals to the art of anesthesia is an ether induction preliminary to tonsillectomy. This may establish in them a well-founded horror of anesthesia for the rest of their lives.

NITROUS OXID

In an effort to obtain better anesthesia in this operation, McKesson developed a technic for using nitrous oxid in the sitting position and reported this in 1915. The pleasant induction and light transient anesthesia afforded by this agent, together with the ease with which reflexes could be restored, and the rapid recovery with minimal toxic effect, removed many of these difficulties. Unfortunately the technic as originally described had certain disadvantages, and never achieved wide popularity. Relaxation of the muscles of the throat was often inadequate and swallowing and gagging annoyed the surgeon. The maintenance of anesthesia on a smooth plane was difficult because the leakage of air into the open mouth diluted and counteracted the nitrous oxid. This could be avoided by the administration of the anesthetic gases through the nose under increased pressure so that air was excluded, but this involved the waste of much gas and increased the cost

considerably. The maintenance of anesthesia in a large, muscular male with nitrous oxid was a problem taxing to the utmost the skill of the anesthetist. Nevertheless this technic was felt to be an advance for McKesson was able to report in 1924 a complete absence of pulmonary or other complications following the use of nitrous oxid.

ENDO-TRACHEAL

It was felt that the endo-tracheal technic would remove many of these disadvantages, for by delivering the agent directly into the trachea much of the dead space would be eliminated and better anesthesia would ensue. This method offered a solution to the problem of air dilution for it was possible then to eliminate leaks. Occluding the larynx by a tube, and packing, if necessary, would absolutely prevent aspiration, and overcome our anxiety over bleeding into the throat. It would also serve to eliminate the bubbling of the anesthetic gases in the mouth which would frequently obstruct the field with sanguinous froth. The endo-tracheal technic would absolutely overcome asphyxia, and no position of the patient or manipulation of the surgeon could produce respiratory embarrassment. Considerable saving in gas would result due to the fact that atmospheric pressures could be used, and waste through the mouth prevented.

Efforts were made to apply the endo-tracheal method to this operation, but more difficulties were encountered. Such deep anesthesia with ether was necessary to perform laryngoscopy preliminary to intubation that the advantages of nitrous oxid were greatly diminished. Several models of introducers were obtained, and others constructed, in an effort to eliminate laryngoscopy, but none was satisfactory. The surgeons complained that the tube in the mouth was a serious obstacle to a good dissection, and if a tube was selected that was so small that it was not in the way, it was difficult to deliver sufficient gas through it to supply the respiratory volume unless increased pressure was used. High intratracheal pressures make expiration difficult, and carry with them the risk of emphysema.

The publication by Magill of his method of blind trans-nasal intubation provided the solution of the problem. It has advantages not to be found with any other technic for very light anesthesia may be used, there is no interference with the surgeon working in the mouth, no laryngoscope or other apparatus is necessary and the procedure may be carried out with ease in home, hospital or clinic.

The catheters used may be made from commercial rubber tubing, varying in size from 9 to 12 millimeters outside diameter, and 25 centimeters long. At one end a bevel is cut at an angle of about 30 degrees, and the other is pierced with a safety pin to keep it from disappearing inside the patient's nose. They are scrubbed inside and out with soap and water (a drinking tube brush is useful), sterilized in mercury cyanide solution, and kept coiled up in a circular box such as contains

motion picture film. They cannot be bitten, do not kink readily and are practically self-retaining.

The technic of introducing such catheters is simple but practice and experience are necessary to be consistently successful. The premedicated patient is placed in a dental chair in the upright sitting position, and kept from slipping down while under anesthesia by ties placed about the shoulders, around the pelvis, and the knees. The sitting position gives the surgeon better exposure, and makes for freer respiration, but the supine position may be used if preferred.

Anesthesia is induced in the usual manner with nitrous oxid, and when a satisfactory plane has been reached the face mask is removed and the largest catheter that will go easily in the most patent nostril is selected. It is well lubricated and passed along the floor of the nasal passage where it is widest. When the proximal end is in the vicinity of the larynx, characteristic tubular breathing will be heard through the catheter. The head is supported in a "headlock" by the left arm, for slight changes in its position will assist in getting the catheter lined up with the larynx. When this is accomplished an attempt is made to introduce the tube when the glottis is open during inspiration. If successful there is usually a characteristic cough and the tubular breathing is continued through the catheter. If the patient does not breathe through the catheter it is not in the trachea. If unsuccessful at the first attempt one should persist, reanesthetizing the patient from time to time should he show signs of recovery from the anesthesia. Often a catheter with a different curve than the original will be more successful, or one with a smaller caliber. The other naris may direct the tube more accurately. Laryngospasm may be produced by the tube stimulating the larynx. This will be terminated spontaneously, often by an energetic gasp, during which the catheter can be easily inserted. If the patient recovers too promptly or if there is undue difficulty in intubation under unsupplemented nitrous oxid, a small amount of ether is added to get more relaxation and give more time for inserting the tube.

If it is still impossible to insert the catheter we either resort to laryngoscopy or use simple insufflation of the anesthetic gases through the nose. Laryngoscopy will usually show us that our difficulty has been in using a catheter with a faulty curve or of too large caliber or that it has been poorly directed due to a deflected septum or some other abnormality of the nose or throat.

After the tube is in position it is connected with the gas apparatus by an adaptor, or else simply covered with the nasal inhaler. The ether, if used, is now turned off. The mouth gag is inserted; if this proves difficult a breath of oxygen will usually provide sufficient relaxation. Two gauze sponges, about the size of walnuts, are placed on each side of the tube, low in the pyriform fossa. Packing may be used if desired. These effectively isolate the larynx from the oral cavity. The surgeon now proceeds with his dissection. He need not worry

about aspiration or asphyxia, but has time to do a careful operation without need to consider the anesthesia. The administration of the anesthetic is greatly simplified; quiet, efficient breathing and adequate rebreathing are obtained at all times and even the resistant, muscular type is handled with ease.

If the adenoids are to be removed the tube is withdrawn after tonsillar bleeding is all controlled and packs removed from the throat, and the anesthesia is continued by intrapharyngeal insufflation through the nose. This is much less efficient but it is not important should the anesthesia become quite light, for recovery is hastened and aspiration of adenoid bleeding is prevented.

Recovery is typical of nitrous oxid. Many can assist themselves from the chair to stretcher, practically all are conscious before leaving the operating room. Vomiting is rare and post-anesthetic depression conspicuously absent.

CONTRAINDICATIONS

We believe that nasal intubation should not be used when there is acute upper respiratory or sinus infection or disease of the larynx. One must be cautious in using too large a tube that could cause trauma to the larynx. The greatest gentleness in inserting the catheter must always be observed, and care taken that the cords are well abducted before any attempt is made to pass the tube. Non-fatty, water soluble lubricating jelly is preferred to vaseline, as it causes no deterioration of the rubber, and does not tend to act as a foreign body should it get into the trachea. It is also more easily removed from the lumen of the tube.

Endo-tracheal is not used if the surgeon takes less than ten minutes, as it is hardly worth while for such a short operation. Nor is it used in babies on account of mechanical difficulties.

STATISTICS

Herewith is recorded one thousand five hundred and fifty nitrous oxid tonsil anesthesias given during the last five years by the author and associates, F. W. Clement, M. P. Cooper and H. H. Stevens. The patients varied in age from three to sixty-eight; the mean of ages was nine years. Fifty-two per cent. were female. Magill's method of blind trans-nasal intubation was used in one thousand one hundred eighty-one cases or seventy-six per cent. It is interesting to note that the percentage of cases receiving endo-tracheal has shown a progressive increase from thirty-six per cent. in 1935 to eighty-five per cent. in 1939. This indicates that the popularity of the method is growing among the surgeons for whom we work, and also reflects our increasing skill in blind intubation. Of the cases where blind endo-tracheal was not done, a small percentage were laryngoscoped. In the remainder anesthesia

was maintained by intrapharyngeal insufflation through the nose either because there was some contraindication to intubation, or failure to insert the catheter readily.

In sixty per cent. of cases intubation was carried out under nitrous oxid alone; small amounts of ether were added in the remainder for better relaxation and to give time for the necessary manipulations. The amount of ether used, and the cases in which it was employed also show a decline, as our skill increases, from sixty-two per cent. to thirty-six per cent.

There were forty-two surgeons represented in this series of whom twenty-one were general practitioners, fourteen oto-laryngologists, and seven general surgeons. The dissection and snare method was used by all but two. The average length of operation was forty-six minutes.

The gas consumption for these tonsil dissections averaged one hundred fifty-two gallons per case; the cost of the anesthesia was, therefore, about a dollar and a half. Post-anesthetic vomiting was rare, and prompt, uncomplicated recovery the rule. Eighty-one per cent. of the cases were out-patients who left the clinic in three to six hours after operation. The small minority who were hospitalized stayed overnight.

COMPLICATIONS

There were no anesthetic or operative deaths. A few patients had hoarseness that lasted a few hours. Epistaxis was produced a number of times by the passage of the catheter but always stopped promptly and caused no trouble. Mucus in the catheter had to be sucked out occasionally to ensure free breathing.

On three occasions, a sponge was overlooked in the throat when the tube was removed. Two of the patients were awake enough to spit it out without trouble. In the other, it impacted in the larynx and caused considerable asphyxia before it was removed through the laryngoscope. Better cooperation between surgeon and anesthetist has prevented a recurrence of this accident.

One child developed laryngeal edema due to an attempt to pass a catheter that was too large. The patient was hospitalized for observation but recovered promptly without treatment except inhalations of steam.

We had hoped to be able to report this series without any incidence of pulmonary complication, but last year we had the first since using this method. A boy of six was operated on by an intern, nitrous oxid being given by the nasal endo-tracheal method. There was much hemorrhage, inadequate suction, packs became saturated and were not replaced, and the operation consumed over one and a half hours. There was gross moisture in his lungs following the operation, and the next day an obvious broncho-pneumonia. Fortunately recovery was prompt. There were no other pulmonary complications of any kind.

SUMMARY

Anesthesia in tonsillectomy presents problems in that most of the patients are children, and asphyxia, aspiration and post-anesthetic depression are common. These can be overcome by the use of nitrous oxid, but the technic is difficult unless endo-tracheal inhalation is used. The author's method of blind trans-nasal intubation is described. One thousand, five hundred and fifty nitrous oxid tonsil anesthesias are recorded in which a nasal endotracheal technic was used in one thousand, one hundred and eighty-one, or seventy-six per cent. The incidence of pulmonary and other complications was very low.

2228 ASHLAND AVENUE

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2. McKesson, E. I.: Pure Gas-Oxygen Anesthesia for Ear, Nose and Throat Surgery, J. A. M. A. 83: 1502 (Nov. 8) 1924.
3. Magill, I. W.: Endotracheal Anesthesia, Tr. Royal Soc. Med., 1928.

The Nineteenth Annual Congress of Anesthetists will be held in Chicago, Illinois, October 21–25. This date corresponds with the Congress of the American College of Surgeons. The Headquarters, Sessions, Exhibits, and Annual Banquet will be held at the Congress Hotel on Michigan Boulevard. The Congress will consist of Sessions of scientific papers, Anesthesia clinics, and laboratory demonstrations, exhibits of newer anesthetics and apparatus and entertainment for the visiting ladies. Further information may be obtained from Charles J. Wells, M.D., Chairman, Congress Committee on Program and Arrangements, 1932 South Salina Street, Syracuse, New York.

EDITORIAL

The Sword of Damocles, suspended by a hair over the anesthetist and his patient, has a keen edge, deficiency of oxygen; and a sharp point, excess of carbon dioxide. Terminology often obscures an otherwise clear picture. The word "asphyxia" by derivation, means to cease throbbing or pulsating, but the dictionary now defines it as a deficiency of oxygen and an excess of carbon dioxide in the blood. Cyanosis, gross evidence of lack of oxygen in the blood, is often mistakenly used as a synonym for asphyxia. Asphyxia entails both lack of oxygen and an excess of carbon dioxide; cyanosis represents but half the picture. Some anesthetists and even a few physiologists fail to recognize the difference between these two terms. With the increasing frequency of use of sedative and narcotic drugs, which tend to depress and obstruct respiration; with the therapeutic application of a variety of agents administered by inhalation which may stimulate, depress or have no effect on respiration; and with the frequent employment of technics which involve changes of gaseous tensions of the inhaled atmosphere, we make effective many variables and produce many conditions that are truly abnormal. Because of these variables, modern anesthetists must become cognizant of the dangers encountered when carbon dioxide is allowed to accumulate in excess or when a deficient supply of oxygen is administered to a patient. He must make a sharp distinction in his own mind between these two physiologic conditions if he is to guard properly the patient's welfare and if difficulties are to be avoided.

Not infrequently illness, injury, or the surgical procedure cause more or less interference with the extensive "transport system" which carries oxygen from the environmental atmosphere to the tissues and carbon dioxide from the tissues to the atmosphere. Familiarity with the undesirable pharmacologic characteristics of agents administered for the relief of pain whether they be volatile or non-volatile or whether they act locally or generally is important because certain factors of all such drugs influence, either directly or indirectly, the transportation of oxygen and carbon dioxide. Disturbances of the reflex mechanisms originating about the pharynx and larynx are recognized by anesthetists as sources of respiratory embarrassment. Obtundation of the cough reflex and ciliary activity is associated with a failure to clear the air passage. Consequently obstruction, partial or complete, occurs.

This syndrome is less frequently appreciated in its incipient stage. The various pieces of apparatus designed to control the concentration of gases inhaled by patients during maintenance of anesthesia are potentially dangerous. Such machines may be used by those who are not keenly aware of the physical signs associated with mild deficiency of oxygen or excess of carbon dioxide and patients may suffer permanent damage.

To compensate for deficient transportation of oxygen by the administration of atmospheres containing a high tension of oxygen is laudable. However, the satisfactory color of patients inhaling atmospheres rich in oxygen may influence us to overlook the presence of respiratory acidosis induced by the deficient elimination of carbon dioxide.

That slender hair suspending the Sword of Damocles will be transformed into a stout cord if those, who undertake the relief of pain, thoroughly appreciate the distinction between deficiency of oxygen and excess of carbon dioxide, and if procedures likely to maintain or restore normal tensions of each gas in the tissues of the body are employed.

Anesthesiologists who are interested in the preparation of a scientific exhibit on any phase of this specialty should apply to Thomas G. Hull, M.D., Director of Exhibits, American Medical Association, 535 N. Dearborn Street, Chicago, Ill., for space in the Scientific Exhibit at the Cleveland Scientific Assembly of the American Medical Association to be held in June, 1941.

BOOK REVIEWS

Principles of Surgical Care—Shock and Other Problems. ALFRED BLALOCK, M.D., Professor of Surgery, Vanderbilt University School of Medicine, Nashville, Tenn. 325 pages and 13 illustrations. St. Louis: The C. V. Mosby Company, 1940. Cloth—price $4.50.

The anesthesiologist is a vital part of the surgical team of today. Upon him rests a share in the responsibility of evaluating a surgical risk as well as in the selection of the anesthetic agent best fitted for a given case. He not infrequently is and can be more frequently a valuable consultant in the post-operative management. Bearing in mind these few simple facts, Dr. Blalock's book, while written by a surgeon primarily for the surgeon, may well be read by the specialist in the field that is only recently assuming its rightful position of importance in the surgical set—the anesthesiology.

Dr. Blalock represents the modern school of the physiological surgeon for it may well be said that surgery is now in the physiological era. Following the Listerian period improvements in technique were rapid and resulted in a wider field of surgical attack. More recently the most valuable advances have been made along the lines of physiology with an increasing knowledge of the disturbances of physiology in relation to disease. By the practical application of this increased knowledge have come the appreciable reductions in the morbidity and mortality from surgical procedures. This present volume by Dr. Blalock embodies a review of the highlights of physiological knowledge in relation to the surgical patient, both pre- and post-operatively. Dr. Blalock's contributions to medical literature, particularly in the field of shock, are well known and it is around this central theme that he has so clearly elucidated the many contributory factors that bear a close relation to shock in the surgical patient. Quoting from Cutler and Zollinger, the ideal consideration surrounding the satisfactory surgical risk permits a patient to come to operation with tissues adequately supplied with fluids, the food reserves in their normal state, the metabolism adjusted as perfectly as it may be, the intestines working normally, the circulation at its optimum level and a nervous system as undisturbed and peaceful as in daily life. I can think of no better summary for the scope of Dr. Blalock's work than this quotation: "For in each of the various phases above mentioned he has given us the most timely advances in medical literature."

Disorders of the circulatory system occupy three chapters, the first applying to the heart, the second to thrombosis and embolism, and the third to peripheral circulatory failure or shock. This is the largest chapter in the book and there are 246 references in the bibliography to this chapter alone, attesting to the careful researches that typify the entire work.

Fluid and electrolyte disturbances and disorders receive appropriate attention, as do those of acid-base disturbances, along with nutritional and metabolic disorders. The importance of anesthesiology and its relation to disturbances in vital economy are stressed. Herein, the importance of anoxia receives its proper evaluation. The importance of surgical technique stressing the Hallsteadian principles is recognized in a chapter devoted to this

subject. Postoperative pulmonary complications receive thoughtful consideration as do those arising in the abdomen.

It is my belief such a work could well be used as a basis for a lecture course to medical students, impressing upon them the value of the basic sciences in relation to surgery. The tyro in medicine is frequently to want to place undue importance in the operative feat rather than in the sound judgment based on a well founded knowledge in physiological principles. This valuable work can be read and re-read by all members of the surgical team whose constant strive should always aim toward better attainment.

E. H. D.

The Library and Museum of The American Society of Anesthetists, Inc., are located at 745 Fifth Avenue, Room 1503, New York City. Reference books, pictures, apparatus, and other gifts have been received. Additional books and funds are needed to establish a loan division.

The American Society for Regional Anesthesia, Inc., announces the Labat Memorial Research Fund contributions should be sent to Paul M. Wood, M.D., Secretary-Treasurer, 131 Riverside Drive, New York, New York. Such contributions are deductible from Federal income taxation.

ABSTRACTS

Editorial Comment: A fixed style of presentation for this department of ANESTHESIOLOGY has purposely not been defined. It is the wish of the Editorial Board to provide our readers with the type of abstract they desire. Correspondence is invited offering suggestions in regard to the length of abstracts, character of them, and source of them.

DONALD E. BRACE. *The Significance of Oxygen to the Surgical Patient.* West Virginia M. J. 36 (February), 1940.

"In the early eighteenth century the work of John Black, of Edinburgh, proved that carbon dioxide was given off by the lungs during respiration. In 1774 Joseph Priestley isolated what he termed a 'new air' and reported this experimental work before the Royal Society. . . . In this same report Priestley suggested the use of oxygen for the purification of atmosphere and for the treatment of patients suffering from respiratory disease. That is, I believe, the first reference advocating the use of oxygen as a therapeutic agent. He also discovered at this time that oxygen was necessary to convert venous into arterial blood. Shortly afterward the monumental contribution of Lavoisier appeared and he it was who gave this new air of Priestley's the modern name of oxygen. . . . In 1812 Legallois established the site of the respiratory center. The brilliant work of Hering and Breuer established the reflex now known by their names. Also important was Pfluger's conclusion that both excess of carbon dioxide and want of oxygen excite the respiratory centers which paved the way for the Meischer-Rusch theory that the chemical regulation of the respiratory center is governed by the carbon dioxide tension of the blood. . . .

"The significance of oxygen to the surgical patient becomes obvious when the supply of this vital gas to the organ and tissue cells becomes less than their requirements. . . . One understands by the term anoxia a deficient supply of oxygen available to the cells of the body. . . . Anoxemia on the other hand is a decreased oxygen content of the blood. These, as listed by Barcroft, are as follows: (1) . . . The anoxic type in which the tension of alveolar oxygen is lowered, such as occurs on mountain tops. The tension of the oxygen in the arterial blood decreases in proportion to the change in alveolar oxygen tension. This type is observed frequently during surgery and is usually very destructive in its effects. It is associated clinically with conditions such as pneumonia, pulmonary edema, fatigued respiratory center, etc. This type of anoxia has sufficient volume of oxygen but its tension is too low for diffusion into tissue spaces. (2) . . . The anemic type in which anoxia arises from a decrease in the quantity of functioning hemoglobin. Both the tension and quantity of oxygen are normal. This type occurs during anemias, carbon monoxide poisoning and methemoglobinemia, etc. (3) The stagnant type: . . . in which the blood flow through the capillaries is too slow and as a result there is an inadequate oxygen supply for the tissues. This form is not infrequently observed following hemorrhage, shock, and local conditions associated with congestion. (4) . . . The histotoxic type in which the tissue cells are un-

able to use the oxygen because of the dysfunctioning of the cellular processes. In our own clinical activities we have heretofore given supplemental oxygen to patients when an inadequate supply was existent, confident that the increased volume of the gas would correct this faulty metabolism. No thought was given to the inability of the cell to use this oxygen once the supply had been augmented. . . . The work of Szent, Gyorgyi, Dische, Myerhof and Parniss has increased our knowledge of the complexities of the tissue utilization of oxygen and one may hope therefore that it should be possible for future clinicians to correct the faults of cellular oxygen utilization and to close the gap now existing in oxygen therapy. . . . Anoxic effects on the surgical patient create more difficulties for the surgeon than any other disturbing factor. . . .

"Oxygen constitutes nearly 21 per cent. of the gases in the atmosphere and exerts approximately 155 mm. of partial pressure. After mixing with alveolar air which has lost some of its oxygen to the venous blood, the tension of the oxygen is reduced to 105 mm. and constitutes only 14 per cent. of the gases present. Under normal conditions this head of oxygen will saturate 95 per cent. of the blood leaving the lungs, the hemoglobin of which will be transporting oxygen at the rate of 19.2 c.c. to every 100 c.c. of blood, while its plasma constituent will contain about 0.3 c.c. of oxygen in solution. . . . The oxygen combined with hemoglobin acts only as a reserve to maintain the fractional contents of that in the plasma, since the plasma releases its oxygen in physical solution to replenish that of the cells which is constantly being exhaused by their functional activity. The oxygen combined with hemoglobin must therefore enter into solution in blood plasma before being delivered for tissue utilization. . . . The effects of oxygen deprivation depend upon the speed of its development, the degree in which it exists, and its duration. . . . Lowenberg, Waggoner and Zbinden, Caine, Davis and others have emphasized the pernicious effects of anoxia on the brain in nitrous oxide anesthesia. Three reported cases showed destruction of the cortex and basal ganglia. Courville has reported on 13 cases with nine deaths showing: (*a*) Sclerosis of scattered pyramidal cells, (*b*) discrete pale areas in the cortex, (*c*) necrosis of cortical layers and subtotal destruction of the cortex. . . .

"The heart, kidneys and other organs likewise show the effect of oxygen deprivation, but the brunt of the attack is directed to the brain and heart, which are the least tolerant of its existence. The heart muscle is extremely sensitive to oxygen deficiency. Normal function ceases when oxygen debt amounts to 0.66 c.c. per gram of cardiac tissue, which is one-fifth of the tolerance exhibited by skeletal muscles. . . . A computation of the amount of oxygen consumed from cerebral blood flow was made by Lennox, Gibbs & Gibbs in an attempt to show the degree of saturation of oxygen in venous blood necessary to produce an unconscious state. Tests were made on unanesthetized human subjects from the blood returning from the brain in the jugular veins. Analysis showed that when the oxygen saturation fell to 24 per cent. or less unconsciousness intervened. . . . Quaestel suggests that the respiratory activity of the brain is restricted in its use of metabolites. Glucose constitutes the most important substance used and therefore its presence as well as that of oxygen is imperative for physiological activity and their supply must be constant and continuous. . . .

"The more severe types of anemias never become cyanosed even when there

is a large deficit in oxygen, while cases of polycythemia vera manifest an extreme degree of cyanosis while there is an abundant supply of oxygen in circulation available for tissue use. . . . One cannot therefore escape the conclusion that the prevention of anoxia is the most valuable method of approach and with this end in view Waters, Wineland and Seevers have grouped concisely the anoxic causes particularly pertinent to the surgical patient as follows: (1) High metabolic rate due to fever, fear, toxemia, and pain. (2) Reduced pulmonary alveolar surface due to disease or mechanical compression from position. (3) Poor oxygen carrying power of the blood. (4) Cardiac insufficiency. (5) Obstruction of respiratory tract due to: (*a*) Wet lung, secretion of mucus, inhaled fluid, or vomiting; (*b*) laryngospasm; (*c*) defects in anesthetic apparatus. (6) Anesthetic technique (unwise control of gases). (7) Respiratory depression. (*a*) Deep anesthesia; (*b*) high spinal block; (*c*) central depression as with opium and derivatives of barbituric acid. . . . It might be mentioned that the construction of a bronchus or other bronchial traumas may set up pulmocardiac reflexes resulting in cardiac inhibition and even exitus as has been observed by Sauerbruch. These accidents masquerade as respiratory difficulties and may be taken for rapidly developing anoxia. However, they are the result of vagovagal reflexes and can be prevented by atropine medication. . . .

"Finally one might mention briefly the high value of oxygen therapy in the treatment of abdominal distention the details of which are fully described by Fine, Hermanson and Frehling. . . . An adequate supply of oxygen during anesthesia is imperative and a supplemental oxygen supply in preoperative and postoperative conditions is worthy of wider application." J. C. M. C.

BOLAND, E. W.: *Oxygen in high concentrations for relief of pain.* J. A. M. A. **114**: 1512–1514 (Apr. 20), 1940.

This paper deals with the treatment of patients with coronary thrombosis or severe angina pectoris. There are two immediate objections in the treatment of these patients, namely, the support of the circulation and the relief of pain. Oxygen is beneficial in sustaining cardio-respiratory function, especially when significant degrees of shock or pulmonary edema exist, but it has not been widely recognized that inhalation of oxygen in high concentrations is effective in alleviating the pain associated with coronary thrombosis and angina pectoris.

The pain of coronary thrombosis varies in intensity; its severity depends upon the size of the vessel occluded, the speed of occlusion, the adequacy of coronary arterial anastomoses, the activity to which the myocardium is subjected, the sensitivity of the patient to pain and other factors.

In the vast majority of cases pain is adequately controlled by administration of the derivatives of opium, and oxygen in these cases is unnecessary unless symptoms of cardio-respiratory impairment are present. If large doses of opiates fail to relieve pain, the employment of oxygen at concentrations of from 80 to 100 per cent. becomes an important therapeutic adjunct.

Oxygen in high concentrations may also be used in those cases of coronary sclerosis where rest and nitrites fail to control the discomfort which may come with the slightest exercise.

In 1929 the oxygen tent was used but severe pain is seldom alleviated with concentrations of 40 to 60 per cent., so with the advent of the B. L. B. mask, concentrations of 80 to 100 per cent. were possible, and dramatic abatement of the pain may be produced.

The anoxemic or ischemic theory of coronary pain is further upheld by the fact that this pain may be relieved by 100 per cent. oxygen. Boothby has pointed out that administration of pure oxygen increases the oxygen content of arterial blood by from 10 to 15 volumes per cent. In coronary thrombosis the myocardial anoxemia is evidently partially overcome by the delivery of hyper-oxygenated blood through the collateral coronary circulation. In cases of coronary sclerosis with angina pectoris the mechanism is obvious.

In cardiac cases no pulmonary irritation has been noted when 100 per cent. oxygen was used, even after three, four, or five days. Thus administration of oxygen in high concentrations serves as an efficient method of relieving the intense pain which may accompany acute coronary thrombosis and as an important therapeutic adjunct in the symptomatic control of severe angina pectoris.

C. H.

BOGRAD, NATHAN: *A method for initiating respiration in the newborn.* South. M. J. **33**: 531–532 (May) 1940.

"Following delivery of a newborn in whom respiration could not be initiated by artificial respiration, an attempt was made to clear out the passages. It was somewhat difficult to open the mouth. The finger covered with gauze forcibly opened the mouth, and doing so stroked the palate perhaps more harshly than was necessary. The baby gasped, breathed several times and stopped. Curiosity was aroused as to whether this was coincidental or whether the opening of the mouth or stroking of the palate was responsible. The hard palate was again stroked several times, the infant cried and respiration was established.

"It was decided to try this method on succeeding deliveries. Of the next eleven cases all but one were delivered in a hospital. All mothers received barbiturate, hyoscine hydrobromide and ether with the exception of the home delivery, who received barbiturate only. The response to palatal stimulation was either immediate in the mildly asphyxiated infants or after two to three minutes in the deeper forms. Stroking the palate exhibited a delayed reflex involving the abdominal muscles. The movement of these muscles might stop after a few excursions and could again be started by similar stroking. Rarely was the outcry present. That the 'act of respiration' had begun could be noted by the rhythmic contractions of the abdominal muscles and changes in the skin color with the increasing oxygenation.

"In a case where the asphyxia was light and respiration would have started without any stimulus, stroking of the hard palate caused flexion of both the upper and lower extremities with a sharp outcry. In home delivery, after respiration had begun and the baby had been put aside, a neighbor drew my attention to the grunting and abnormal rhythm of the respiration. Brushing the palate quickly changed the rhythm to normal. . . .

"There were no abrasions of the palate and suckling was not interfered with. The method is superior to the older forms of stimulation, since it will not lead to excessive heat loss, shock and other complications." Bibliography—5 references.

J. C. M. C.

FANTUS, BERNARD AND SEED, LINDON: *The therapy of acute peripheral circulation failure: syncope, shock and collapse.* J. A. M. A. **114**: 2010–2015 (May 18) 1940.

"Acute circulatory failure may be of three etiologic types: It may be due to heart failure (q.v.), to hemorrhage

(q.v.) or to failure of the peripheral circulation. . . .

"In the type due to hemorrhage, the filling of the depleted vessels is of prime importance and, when this is due to loss of blood volume, prompt blood transfusion is the remedy. In this condition vasoconstrictor drugs may do harm.

"Failure of the peripheral circulation includes a number of clinical syndromes characterized by inadequacy of circulating blood volume (absolute or relative) due to causes other than hemorrhage. In traumatic shock there is practically always loss of blood, but this is insufficient in degree to cause the clinical picture.

"The insufficiency of circulating blood volume results in a great decrease in venous return flow and hence of cardiac output, a fall in arterial and capillary pressure, a small pulse pressure and an anemic anoxia of all the organs, most significantly of the brain. The reflexes are decreased or abolished. The skin is ashy gray and is covered with cold perspiration. This failure of the peripheral circulation may be of most complex causation and is perhaps best discussed under the traditional clinical concepts of syncope, shock and collapse, provided these terms are given definite meanings, which they at present by no means enjoy. We shall here distinguish between syncope, traumatic shock and collapse. . . .

"Syncope, neurocirculatory failure, fainting or swooning is a sudden and, unless quickly fatal, transient form of general systemic depression, characterized by an unexpected, partial or complete suspension of consciousness and of locomotion and often of circulation and respiration.

"Failure to maintain an adequate cerebral circulation is due to psychic or reflex (i.e. neural) influences affecting cardiac and vascular functions. This neurogenic collapse may be of several types: (1) vasovagal syncope, (2) vasal syncope, (3) cardiac syncope and (4) carotid sinus syncope.

"All these types are characterized by their transient natures (unless the patient dies, which may happen) and by the absence of marked hemic or chemical changes.

"*Vasovagal syncope* . . . is the most common type. It is the ordinary 'fainting spell' and is due to a combination of vasodilator and cardio-inhibitory actions which results in a greatly diminished return of blood to the heart. It occurs most commonly in predisposed persons suffering from vasomotor instability and a tendency to postural hypotension, which may be constitutional or acquired, as from prolonged bed rest, debilitating conditions such as fatigue, fasting, anemia or other disease. The precipitating factors, acting most especially by producing splanchnic vasodilatation, are prolonged standing in crowds, sudden getting up after prolonged recumbency, or the rapid withdrawal of large quantities of fluid (e.g. 'tapping' of ascites). If under these conditions vagus stimulation occurs as the result of fright, pain or other profound emotion, the patient loses consciousness. Reflex stimulation from almost any instrumentation or from a blow on the solar plexus produces the same result. When the patient falls, the resultant low position of the head remedies the cerebral anoxemia and revival takes place, though the weakness continues for some time thereafter. . . .

"Stability of the vasomotor system should be improved and anemia or any other systemic abnormality should be rectified. . . . During instrumentation of any kind the sitting posture should be avoided, especially by weak patients. Preoperative administration of sedatives and local anesthesia prevent syncope. Thus, prior to pleural operations the patient should receive from

0.10 to 0.20 Gm. of soluble phenobarbital and 1 mg. of atropine subcutaneously. Local anesthesia should be applied not only subcutaneously but also intrapleurally.

"Since, in contradistinction to the normal, the circulation in syncope is affected by gravity, the head-down or 'shock' position should promptly be assumed and the legs elevated. The clothing should be loosened. Reflex stimulation may be secured by applying cold water to the face or by cautiously inhaling ammonia vapor, preferably from aromatic spirit of ammonia. Inhalation of oxygen with 10 per cent. carbon dioxide may be helpful. Intravenous administration of 1 mg. of atropine sulfate or of 1 cc. of epinephrine in 1:10,000 solution may result in instantaneous recovery. In profound syncope subcutaneous injection is of no use because of poor absorption. Artificial respiration and heart and thoracic massage should be promptly resorted to if the condition seems desperate. The patient should be permitted to lie down until fully recovered. Against the consecutive headache one may use acetylsalicylic acid or another analgesic.

"*Vasoconstrictor syncope* . . . occurs from stimulation of the vasomotor center by chemical or mechanical agents. Most characteristic of this type is the syncope following administration of a local anesthetic in which the patient, usually, sitting in the dentist's chair, collapses, may have convulsions and may even die.

"The therapy is in many respects similar to that of the vasovagal type. The administration of barbiturate is prophylactic and the slow intravenous injection of soluble phenobarbital (0.50 Gm.) may be life saving during an attack. Administration of epinephrine is contraindicated in this condition. . . .

"Cardiac syncope . . . occurs whenever the output from the heart is insufficient to maintain an adequate blood supply to the brain. It may be vagal syncope, which occurs typically in the Adams-Stokes syndrome: 'syncope plus slow pulse' sometimes accompanied by convulsive seizures. . . . Cardiac syncope also may occur in paroxysmal tachycardia as well as in angina pectoris and in congestive heart failure. . . .

"*Carotid sinus syncope* . . . may be vasal or vagal. The function of the carotid sinus (a bulbous dilatation rich in sensory nerves located at the bifurcation of the internal carotid artery) is to prevent undue rise of arterial pressure and excessive increase of heart rate. Its stimulation results in cardioinhibition and/or vasodilatation. Hypersensitiveness of the carotid sinus or organic lesions in its vicinity may result in spontaneous syncope, attacks of which may be induced in such cases by pressure on the carotid sinus, which is pathognomonic of such hypersensitiveness. There are three varieties of carotid sinus and syncope: one in which the pulse is markedly slowed, a second in which the blood pressure drops profoundly and a third in which convulsions are produced.

"In addition to placing the patient in the horizontal position and loosening the clothing, particularly around the neck, the administration of epinephrine is indicated. Atropine is especially useful if the pulse is markedly slowed. . . .

"Traumatic shock, as it is seen in hospitals, should be defined as a depression of the vital processes consequent on severe physical injury and due to a great insufficiency in volume of circulating blood, which may be partly due to actual loss of blood to the exterior into some of the body cavities or into the soft tissues and partly or entirely due to 'plasmosis,' i.e. exudation of blood plasma into the injured

area. This is what is commonly called 'secondary shock.' What is called 'primary shock' is syncope, being characterized by suddenness of onset and a tendency to recovery (reaction), especially in the head-low posture. Shock may insensibly pass into vasodilatation collapse (q.v.). . . .

"From a clinical point of view, the most important definite factor in the diagnosis and treatment of traumatic shock is the low blood pressure. One continues treatment governed largely by the effect of the treatment on the blood pressure. . . .

"The so-called primary shock is essentially syncope. It is more severe in adults than in children and in nervous than in phlegmatic persons, and is also severe in persons crippled by organic disease; it is more prone to occur under the influence of hunger, fatigue, exposure, fear and terror. . . . The more sensitive the tissue damaged the more nerves are involved in the injury, or the larger the nerve injured the greater is the degree of shock. This is the reflex (syncopal) factor.

"The 'reaction' stage usually sets in within a few hours if the condition is not speedily fatal. The reaction is possibly due to a number of influences: the waning of the syncopal factor, or the vasopressor action of accumulating carbon dioxide and of adrenal secretion. Marked delay in the onset of the reaction should cause one to look for complicating hemorrhage (q.v.), hemoconcentration collapse, . . . or acidosis (q.v.). The reaction sets in with the return of color to the face, the pulse becomes slower and stronger and the temperature rises, sometimes above normal. Vomiting may usher in the reaction. If vomiting occurs during the first stage, it is a bad omen.

"The stage of 'secondary shock' may supervene on the reaction or on alternate periods of reaction and depression. The secondary shock is usually due to hemorrhage and/or exudation. In either case the reduction in the volume of circulating fluid results in stimulation of the vasomotor center, so as to maintain a degree of circulatory activity compatible with life. Under these circumstances the vasomotor center keeps, by splanchnic vasoconstriction, the blood pressure higher than it would otherwise be. If in spite of this the blood volume continues to fall, the condition passes insensibly into 'vasodilatation' collapse from failure of the vasomotor center due to inadequate blood supply, and now the splanchnic blood vessels dilate. When this occurs, and especially when in addition these vessels have become leaky as a result of prolonged impairment of their nutrition, the condition is fatal, responding to no therapeutic efforts. The practical lessons to be drawn from these considerations are, first, that for a patient in shock, as also for the patient in hemorrhage, general or subarachnoid anesthesia is extremely dangerous because of their vasodilator tendencies. Secondly, promptness is an essential factor to success in treatment. If the correct treatment is not applied at the right time, no amount or kind of treatment will do any good. . . .

"Operation shock, like sepsis, is more easily prevented than treated once it has occurred. It is the debilitated patient who is the most likely to have operation shock. A debilitated patient is one who has a loss of strength or loss of weight or anemia or all three. These are the three most important criteria of tendency to shock. Proper preparation of the patient tends to secure optimal resistance and reserve. . . .

"Expert anesthesia minimizes the causative reflex factor. In some cases morphine 8 to 10 mg. and scopolamine hydrobromide 0.5 mg. hypodermically twenty minutes before operation are useful to combat restlessness and lessen the amount of anesthetic required.

The duration of the anesthesia should be as short as possible. In the presence of shock a local anesthetic is best. Next comes ethylene, and ether comes last in order. During the period of anesthesia it is imperative that an accurate check be made on the blood pressure and pulse rate. Tissue trauma increases shock by increasing the amount of 'exudation': hence tissue trauma must be minimized; so must nerve injury. . . . Psychic shock should be prevented by reassuring, kindly and humane treatment of the patient. . . . Bodily warmth should be maintained. . . . A patient in shock with a systolic blood pressure under 90 should never be operated on unless a continuous blood transfusion is being given during the operation. A continuous transfusion of blood during operation may allow one to do an imperative operation safely on a patient in severe shock. . . .

"In any severe case autotransfusion (bandaging limbs after raising each in turn for a few minutes) may be of value. If hemorrhage is present, it must be arrested as soon as possible and the loss of blood made good by a blood transfusion as promptly and as thoroughly as the occasion permits. Lost body fluid should be restored. . . .

"In profound shock the administration of fluid by hypodermoclysis is relatively futile, because in this condition fluid passes out of the capillaries and, in the presence of shock severe enough to be fatal, fluid thus given is not likely to be absorbed. . . .

"Circulatory stimulants are important. The only drug that may be of any value in the final (vasodilatation) stage of collapse is epinephrine, but unfortunately its effect is so transient —lasting but a few minutes—that it is of value only as a temporary measure to give time for the administration of more valuable measures, such as transfusion. It must be administered intravenously. In extreme emergency, intra-auricular injection of epinephrine 1 to 5 cc. of 1:1,000 solution may possibly be life saving. . . .

"Collapse is a condition of extreme prostration due to (1) absolute or (2) relative insufficiency of blood volume without actual loss of blood. It is of slower onset than syncope or shock and of indefinite duration. . . .

"Prophylactic therapy . . . is of greatest importance, as treatment is often futile once advanced collapse is present. Therefore every possible effort must be made to discover early the tendency to collapse and to treat correctly the underlying condition, whether this is infection, intoxication, systemic hypohydration, chloride deficiency or plasmosis. . . . Absolute rest is indicated with the head low to keep the blood in the vital centers. 'Autotransfusion' by elevation and centripetal bandaging of the limbs and compression of the abdomen may be tried. . . .

"Hot stimulating drinks (coffee or tea), if the patient can swallow, should be given in small quantities frequently repeated. . . . If the body temperature is subnormal, external heat is the single most important stimulant. . . . Fluid of some sort must be administered, and usually parenterally, as absorption from the gastro-intestinal tract is very poor. . . . Correction of disturbed circulatory mechanics is usually spoken of as 'stimulation.' An estimate should be made of the relative participation of the heart, the blood vessels, the endocrines and the nervous system in the existing depression of the circulation. . . . The respiratory conditions should be improved. If cyanosis supervenes, oxygen inhalation, possibly with 5 per cent. carbon dioxide to act as a respiratory stimulant, may be employed; but it should not be used as a routine before death because it adds to the discomforts of the dying and besides, it would be a waste of expensive gas. To

be of value it must be used early; it should be remembered that collapsed patients become gray from cyanosis rather than blue. Artificial respiration may be resorted to in an acute emergency if breathing becomes enfeebled or irregular." Bibliography—1 reference.

J. C. M. C.

TOVELL, R. M., AND PATTERSON, R. L.: *Intravenous therapy: A hospital problem for which the anesthetist may provide a solution.* Current Researches in Anesth. & Analg. **19**: 171–175 (May–June) 1940.

"The method of preparation of intravenous solutions has been a problem in many hospitals. After a series of untoward reactions, a new method for the preparation of solutions is considered or decision is reached to purchase prepared solutions. We feel that the fluid and its method of preparation is only one factor involved in the occurrence of untoward reactions and that methods of administration and the proper care of administration sets also play an important part. Each one must be developed according to a general plan in order to produce a satisfactory setup. . . . All chemicals are purchased in bulk in chemically pure form.

"In spite of the fact that glassware other than pyrex may be satisfactory this grade has been used throughout the process. The plan has been to prepare fresh supplies of stock solutions with the concentration of sodium chloride and dextrose ten times as great as in the finished product which is administered to patients. These concentrated solutions are diluted with fresh, distilled water in a mixing chamber. From the mixing chamber the solution is measured into pyrex flasks in which it is sterilized and then stored. In order to facilitate this general plan, sodium chloride and dextrose are weighed out in proper quantities and sent to the preparation room in glass stoppered bottles. Physicians attached to the department of anesthesia are responsible for the preparation of the stock solutions, and graduate nurses assigned to the task are responsible for diluting these solutions, filling the flasks and sterilizing them. The department of anesthesiology bears the responsibility involved in the administration of fluids intravenously. . . .

"All glassware used in preparing and diluting stock solutions is washed daily with soap and water and then rinsed with distilled water, following which it is autoclaved. When empty flasks are returned from the wards, they are first rinsed over a fountain spray and then filled with potassium dichromate cleansing fluid. . . . The enamel ware, rubber bushings, steel stoppers, and funnels are thoroughly cleansed in similar manner. . . .

"Only three stock solutions are regularly prepared: (*A*) Sodium chloride 8.5 per cent. in distilled water. (*B*) Dextrose 50 per cent. and sodium chloride 8.5 per cent. in distilled water. (*C*) Dextrose 50 per cent. in distilled water. Bottles containing 1,000 grams of dextrose or 170 grams of sodium chloride are procured from the pharmacy, and with these quantities, stock solutions are prepared in 2,000 cc. lots or multiples thereof. . . .

"The finished product is made up in batches of 9,000 cc. in a mixing chamber. To make up a solution of glucose 5.0 per cent. in physiologic saline, 900 cc. of stock solution is measured out into a graduate and aspirated into the mixing chamber. Sufficient freshly distilled water is then aspirated to fill the mixing bottle to the 9,000 cc. mark. The suction line is detached from the mixing bottle and 1,500 cc. of solution is allowed to flow into a thick-walled flask. The rubber bushing is applied and the steel cap is inserted, but with

the steam vent left open. The flask is labelled and is then ready for sterilizing along with the other flasks in the batch. . . .

"The solutions are autoclaved at 20 pounds pressure for 15 minutes. When they are removed, the steel cap is inserted completely to close the steam vent and as the solutions cool, a vacuum is created. . . . The flasks may then be stored or distributed to the wards. When the solution is to be administered, the steel cap is removed, and a glass vent tube connected to the delivery tube is inserted. The flask is inverted through the vent tube, air gains admission to the flask and the solution flows into the patient's vein. The rate of flow may be controlled by means of an adjustable clamp on the delivery tube. . . .

"Untoward reactions following the administration of fluids prepared in this manner have been minimal. The cost has been reasonable. . . . Anesthetists might well interest themselves in providing service of this sort to hospitals." Bibliography—1 reference.

J. C. M. C.

KRAHL, M. E.: *The effect of variation in ionic strength and temperature on the apparent dissociation constants of thirty substituted barbituric acids.* J. Phys. Chem. **44**: 449–463 (April) 1940.

"By means of glass electrode pH measurements, the effects of variation in sodium chloride concentration of the pK' values of thirty substituted barbituric acids have been determined at 25° C. With concentrations of sodium chloride up to 2 molar, the relation between pK' and the ionic strength is approximately expressed by one form of the Debye-Hückel equation. By means of this equation, pK values at 25° C. have been calculated for all of the acids employed.

"The effects of variation in temperature on the pK' and pK values of 5-isoamyl-5-ethylbarbituric acid have been determined at temperatures between 15° C. and 40° C., and the values of the standard free energy change, $\Delta F°$, have been calculated. For this acid in this temperature range the relation between $\Delta F°$ and temperature is expressed by the usual thermodynamic equations, in which $\Delta S°$, the standard entropy change, has a value of -3.1 calories per degree.

"It has been shown that, by means of the experimental data here presented and an equation derived for this purpose, the approximate pK' values of the thirty substituted barbituric acids can be calculated for any ionic strength and any temperature within the physiological range."

The barbituric acids tested were:

5-allyl-5-benzyl,
5-ethyl-5-phenyl,
5-ethyl-5-cyclohexenyl,
5-allyl-5-isobutyl,
5-(B-bromoallyl)-5-(a-ethylpropyl),
5-(B-bromoallyl)-5-(a-methylpropyl),
5-ethyl-5-piperidyl,
5-(B-bromoallyl)-5-isopropyl,
5-ethyl-5-hexyl,
5-isobutyl-5-(B-methylallyl),
5,5-diallyl,
5-(B-methylallyl)-5-propyl,
5-ethyl-5-(B-ethylhexyl),
5-ethyl-5-(B-phenylethyl),
5,5-diethyl,
5-allyl-5-isopropyl,
5-benzyl-5-butyl,
5-ethyl-5-butyl,
5-isoamyl-5-ethyl,
5-amyl-5-ethyl,
5-(a-methylbutyl)-5-(B-methylallyl),
5-benzyl-5-isopropyl,
5-ethyl-5-(a-methylbutenyl-2),
5-ethyl-5-isopropyl,
5-ethyl-5-(a-ethylpropyl),
5-allyl-5-(a-methylbutyl),
5-cyclopentyl-5-ethyl,
5-ethyl-5-(a-methylbutyl),

5-(a, 2-dimethylbutyl)-5-ethyl,
5-cyclohexenyl-1,
5-dimethyl.
Bibliography—12 references.

J. C. M. C.

R. J. MARCOTTE, D. E. CLARK and H. M. LIVINGSTONE. *Further Laboratory Studies with Trichlorethanol.* Current Researches in Anesth. & Analg. 19: 88–94 (March–April), 1940.

"There is very little to be found in the literature relative to the use of trichlorethanol as an anesthetic agent and though it is not new it has been employed rather infrequently. First mention of its hypnotic action was made by Kulz in 1882. In the course of investigations relative to the action and decomposition of chloral hydrate, trichlorethanol was given to animals and a hypnotic effect observed. In this country Hans Molitor in 1937 was undoubtedly the first to investigate trichlorethanol and carry on research with animal experimentation.

"Our investigative studies began with the determination of changes in the blood in sugar, chlorid and nonprotein nitrogen content in dogs during trichlorethanol anesthesia. Of necessity, all animals were given morphin sulphate gms. 0.0075 to 0.045, depending on their size, previous to the anesthetic, to facilitate handling them, the withdrawal of blood samples, and the insertion of a rectal catheter through which the drug was instilled. . . . Doses of 400 to 600 mgm. of trichlorethanol per kilogram administered rectally produced what might be termed complete anesthesia and it was under these doses that operations were performed on dogs without supplemental agents. Amounts ranging from 100 to 1,600 mgm. per kilogram have been given, but in the latter case it was administered with an initial dose of 600 mgm. per kilogram, followed in one hour by additional quantities of 100 to 200 mgm. per kilogram every fifteen to twenty minutes, until a dose of 1,600 mgm. per kilogram was reached. Undoubtedly an initial dose of 800 to 1,000 mgm. per kilogram would have proved fatal. In most of the lethal dose test cases, 700 to 800 mgm. per kilogram resulted in a fatal termination.

"Of six dogs receiving trichlorethanol, and upon which thoracoplasties were performed, all died within twelve hours to fourteen days, but only one death was partly attributable to the anesthetic. Autopsy revealed massive collapse of both lungs. The first animal which was to be depancreatized and to which a dose of 500 mgm. per kilogram was given, died as the abdomen was being opened. Death was typically respiratory in nature. The next two animals to be pancreatectomized received 400 to 350 mgm. per kilogram, and these survived both the anesthetic and the operation. Whenever a laparotomy was performed, biopsies were made of the liver for glycogen content determinations. This procedure was carried out following the technique of Goode, Kramer and Somogyi. In the first few cases, liver glycogen was found to be only 15 to 25 per cent. of the normal content and at once the question arose as to whether trichlorethanol was responsible for this apparent glycogen depletion of the liver. . . .

"Our interest, however, lay chiefly in the change in liver glycogen caused by trichlorethanol. To attempt to determine this, liver biopsies were made in a series of normal dogs, using only local anesthesia. Immediately following this the usual dosage of trichlorethanol was administered and biopsies repeated in one and two hours, and again in 24 hours. For control animals for these determinations, normal dogs were given morphin sulphate gms. .015 per kilogram and biopsies per-

formed at hourly intervals for two hours. We have found in those animals receiving trichlorethanol that liver glycogen in two hours may drop as much as 50 per cent. from the preanesthetic level. In 24 hours the fall reaches 95 per cent., but this marked change is undoubtedly due to removal of food for 24 hours. In the control animals not receiving the general anesthetic a fall was found, but usually to a much less degree. During ether anesthesia, liver glycogen is found to drop to approximately 50 per cent. of normal value. With liver biopsies for glycogen determinations, a portion also was removed for histological examination. In these sections considerable fatty infiltration was found two hours following anesthesia and in 24 hours it had become even more marked. In the control animals a fatty infiltration occurs, but again to a lesser degree.

"Blood chemistry studies have been conducted on practically all animals receiving trichlorethanol. . . . No significant changes have been found in the N.P.N. or chlorid content of blood samples drawn before the anesthetic was given as compared to those two hours following instillation, and those taken 24 hours later. Some variability has been found in the sugar determinations, but these changes are believed to be due to struggling on the part of the animal or to fear. Marked sugar changes have occurred in some of the dogs on which a thoracoplasty was performed and also in those which underwent pancreatectomies. However, it is to be expected that the blood sugar will mount to a considerable degree twenty-four hours following a pancreatectomy in an animal to which no insulin has been given. However, in normal animals which were anesthetized, but which were quiet before the drug was given and upon which no operative procedure was performed, there was little change in blood sugar content. Hepatic function studies were also conducted, the bromsulphalein test being used, and it was found that normal dogs receiving this agent with no surgical measures, suffered no impairment of liver function. In those cases undergoing surgical procedures a retention occasionally was found which varied from 3 to 20 per cent. but which may be due in part to a traumatized liver which occurred during operation. . . .

"On a few animals, bleeding and clotting times have been conducted both before and after administration of the anesthetic, but no appreciable change has been observed. Skin tests have been made with both trichlorethanol and avertin. Undiluted avertin applied directly to the skin caused an area of erythema which cleared in from three to four hours. With undiluted trichlorethanol there appeared a large, glistening, pearly white lesion which was raised about 1 mm. above the surface of the skin and was surrounded by an erythematous border about 1 cm. wide. This pearly area appeared not unlike a phenol burn. In two to three hours only a markedly erythematous area remained which disappeared 24 hours later. Hair was noticeably absent from the site of the lesion twelve days following this procedure.

"Pulse, respirations and blood pressure were studied at fairly frequent intervals. Respirations always were depressed soon after the anesthetic was given. The pulse rate, in most cases, increased ten to twenty points or more and remained at this elevation for several minutes and then dropped to normal levels. A tendency toward tachycardia always seemed to be present during the early phase of the anesthetic. . . . Almost immediately after starting injection of the anesthetic solution, the blood pressure began to fall quite rapidly until it reached a value of approximately 50 per cent. of the

original. Previous to the anesthetic the carotid or femoral arteries were canulated under local anesthesia, using 1 per cent. novocain for this procedure, so that a normal blood pressure and respiratory value could be obtained. . . . Usually about ten to fifteen minutes after the anesthetic had been administered, the blood pressure reached its lowest value and then began a slow but steady rise until the animal reacted, at which time the blood pressure was slightly below the preanesthetic level. . . . Respirations usually become very shallow, but extremely regular, soon after the initial dose. In recovery cases the depth of respiration increased as the reaction stage was approached. In those cases to which a lethal dose was to be given, the respirations became more depressed as the additional portions were added. A slight fall in blood pressure also occurred, but at times this was imperceptible. As the limit of tolerance was reached, respirations suddenly became irregular and, after a few breaths, ceased entirely. The heart continued to beat for three to five minutes with a steady fall in blood and pulse pressures until a zero level was reached and the heart was no longer active. . . . Microscopic examination of heart, liver, spleen, kidney, and colon of dogs treated with trichlorethanol failed to disclose any significant findings." Bibliography—10 references.

J. C. M. C.

H. R. HULPIEU, J. H. KITCHEL AND J. H. WEATHERBY. *A Comparative Study of Twenty-five Alkylthiobenzoates with Respect to Surface Anesthesia, Toxicity and Systemic Effects.* J. Pharmacol. 68: 395–405 (March), 1940.

Twenty-five alkylthiobenzoates were studied for surface anesthetic activity, toxicity, irritation, and systemic effects. All were found to possess some surface anesthetic activity, but only one appears to be deserving of further study. All of these compounds produce profound disturbances of central nervous system function and have more effect on respiration than on cardiovascular function. The only consistent correlation between chemical structure and pharmacologic activity was increase in toxicity with increase in molecular weight. This was most marked when the addition was made between the carboxy group and the amino nitrogen. Alkylthio derivatives of benzoic acid esters are less active and appear to be less toxic than analogous alkoxy compounds.

A. S.

W. E. BURGE AND E. L. BURGE. *The Effect of Anesthetics on the Electrical Potential of the Brain: Further Observations and Demonstrations.* Current Researches in Anesth. & Analg. 19: 102–105 (March–April), 1940.

"One non-polarizable electrode was placed on the scalp as nearly over the motor area of the brain as the receding of the hair would permit, and another on the forearm . . . , and it was found that an electric current of low amperage passed from the positive scalp through the galvanometer in the circuit to the negative forearm. Various conditions affect the strength of this current. It was decreased during rest and sleep at night and increased during the activities of the day. Moderate exercise increased it, while violent and exhaustive exercise decreased it. . . .

"Ether anesthesia decreased the strength of the current and produced a reversal in polarity of the three human subjects studied during surgical operations. . . .

"Goldfish were placed in water in a cylindrical glass vessel between two platinized platinum disc electrodes.

. . . It was found that an electric current of low amperage passed from the electrode nearer the head, through the galvanometer in the circuit of the electrode nearer the tail of the fish. . . . The strength of the current, as in the human, was found to increase when the goldfish became active in swimming, and to decrease when the fish became quiet. Reversal of position of the fish caused a reversal in the direction of the current. When the fish was crosswise in the chamber the strength of the current decreased to zero. If two fish were placed in the chamber the strength of the current increased when their heads were together near the same electrode and decreased when their heads were in opposite directions. Anesthetization of the fish produced a decrease in the strength of the current and a reversal in polarity in deep anesthesia. . . .

"In the present investigation it is shown that the scalp of the unanesthetized, conscious animal is electro-positive and that of the unconscious, anesthetized animal electro-negative. . . .

"Sensory nerve fibers are more susceptible to the action of local anesthetics than are the motor fibers. . . . The sensory side of the nervous system is more susceptible to the action of general anesthetics than is the motor side, as is indicated by the fact that when a reflex can no longer be elicited by the stimulation of a sensory nerve of an anesthetized animal, its peripheral motor mechanism is still active and stimulation of a motor nerve will cause muscular contractions. . . .

"The electrical potential of the brain cortex at any instant is undoubtedly determined by the balance between the incoming and outgoing nerve impulses, or negative charges, passing to and from the brain over sensory and motor nerves. The fact that general anesthetics block the incoming sensory impulses, or negative charges, while the outgoing negative charges are not blocked and can leave the brain, leads to a loss of negative charges during anesthesia; and in this way the negative potential of the brain cortex is decreased, and in deep anesthesia the loss of negative charges may be sufficiently great to render the cortex electro-positive. According to this theory, general anesthetics decrease the negative potential of the brain cortex and produce anesthesia by virtue of their selective action, blocking the sensory nerves, thus preventing the negative charges or nerve impulses from passing to the brain cortex while the motor nerves, being unaffected, conduct negative charges or nerve impulses away from the brain cortex, thus decreasing its negative potential, with resulting anesthesia.

"We are at present interested in decreasing the negative potential of the brain cortex by electrical means, and in this way hope to produce electrical anesthesia, but as yet have not been entirely successful. In sleep, as in anesthesia, the negative potential of the brain cortex is decreased. In fatigue and exhaustion it is also decreased, but in moderate exercise the brain cortex charges up electrically, resulting in an increase in its negative potential."

J. C. M. C.